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## The Henry Simpson Newland Oration.[1]

### MODERN SCIENCE AND CIVILIZATION.


By THE RIGHT HONOURABLE R. G. MENZIES,
*Prime Minister of Australia.*


I WILL not need to tell you that I feel proud of the invitation to deliver an address which honours the great work done by Sir Henry Simpson Newland in Australian medicine. In common with all of you, though I confess without your qualifications for judgement, I have long admired Sir Henry Newland, one of those rare spirits with the secret of combining high professional skill with a broad and noble conception of public duty and of social service; as a surgeon, familiar with the need for precision; as a defender of the medical profession, clearly aware of the importance of preferring facts and solid reason to mere rhetoric. The very thought of his work places upon me a clear obligation to speak to you with such exactness as I can command, and with what I can achieve of that mental balance which has characterized him so conspicuously.

[1] Delivered at the Tenth Session of the Australasian Medical Congress (British Medical Association) at Hobart, March 1-7, 1958.

*This will not be a political speech in the narrow sense.* It will provide no headlines about disarmament, or "summit" talks, or the problems of diplomacy. These matters are of commanding importance, but they are not my theme tonight.

What I want to do is to consider the place of modern science (including military science) in civilization. This *will involve me, and those of you who are patient,* in some examination of civilization itself, and what it means, and whether it is really advancing.

This is a formidable task to attempt in something less than an hour. But it is occasionally worth while to contemplate immense problems and seek to penetrate them a little. "A man's reach should exceed his grasp, or what's a heaven for?"

We are living, as always, in a period in which emotions and prejudices can easily overthrow reason. The enormous developments of applied science have been publicly related to military provision to such a degree that we are in danger of losing the true conception of education and training and of preferring short-range policies to those long views which alone can help mankind along its eternal march.

The twentieth century has been the great century of scientific discovery and application. The basic researches into pure science have been and are little advertised. They are to an overwhelming extent the product of quiet labour by brilliant men not working against the clock but working

against what must appear frequently to be the intractable problems of matter and of force.

More recently, applied science has come into its own. And because applied science produces what we commonly call "practical results", the applied scientist, the technologist, has become widely publicized, and there is a temptation to regard his craft as the one matter worthy of the attention of the scientific mind. This process has been brought to a head by modern developments in the field of warlike preparation. We have fed full on a diet of news about nuclear bombs, thermonuclear bombs, and now satellites, the space vehicles, the Sputniks.

There is a good deal of successful propaganda, heavily though perhaps unconsciously encouraged in our own countries, to the effect that the Soviet Union has outmatched the world in science, and that we must do something about it very quickly if we are not to be overwhelmed and destroyed. All thinking people have given much thought to this matter. That is why I am taking the opportunity of speaking to you about it tonight. Let me at once say two things.

One is that it is a mistake to be even faintly terrified because the Soviet Union has in one aspect or in some aspects of technology got ahead of the rest of the world. It would, in fact, have been a strange thing if it had not done so. Great talent is not the monopoly of any one country.

There is no doubt that the Soviet Union is training a greater proportion of its population in applied science than is any other country. A report made in September last by the Australian Academy of Science shows that, per million of population, the U.S.S.R. is graduating twice as many applied scientists as the U.S.A. These are striking facts. But their significance is to be qualified in two ways.

First, the Soviet Union can conscript young men and women into science at will. If this means a distortion of the pattern of education and leads to a neglect of humane studies, no great concern will be felt by an administration which is purely materialist in philosophy, which rests upon absolute power, which discourages liberal thought or speech, and which practises in relation to other countries an aggressive imperialism of the most unscrupulous kind. We may properly admire its technological achievements. We may properly seek to emulate them. But we are not to show ourselves willing to pay for them in the Soviet coin.

Second, there is much reason to believe that Soviet technological manpower is excessively concentrated upon military production. This may well produce spectacular results which impress all of us and terrify some of us. But if it means that domestic advancement suffers and better bombs are preferred to better bread, the price paid by the Russian rulers for power may prove too high. Russians at home are men and women, after all, with their own hopes and needs and ambitions.

We would therefore do well to preserve our sense of balance and to recall those many aspects of science in which the free world has been and is clearly ahead of the Soviet Union.

My second observation is that there are two aspects of the "Sputnik" exercise. If it is designed to widen the boundaries of scientific knowledge by gathering and recording information from sources outside the world's atmosphere, then it is something that we should welcome and the results of which should be made available to all nations and to all mankind. After all, I have not (except metaphorically) travelled in space myself, but I can imagine that if I did I should realize more clearly than ever that the world is a small place and that its inhabitants must live together if they are to live at all.

No doubt before we are much older more and more satellites will be shot up into space and recordings will occur. Indeed, I have for some time understood that this is one of the designed activities of the International Geophysical Year. Scientifically speaking, I would be no more disposed to regard it as a tragedy that Russia should send up the first scientific satellite than if some Russian expedition had been the first to reach the South Pole or scale the slopes of Everest. But the real fear that besets us is that the satellite should be developed into a military weapon, so that distant targets may be clearly seen and accurately attacked. One cannot but reasonably suspect that one of the principal propaganda purposes of these recent exercises is not only to induce admiration for Russian applied science but also to strike fear into hearts and induce minds to yield to the spread of communist doctrines and practice. If I am right in this, then the statesmen of the free world have two tasks.

One is the task of themselves maintaining such a power of destruction in war as will deter aggression. It is hard for me to understand those who would seek to abolish nuclear and thermonuclear weapons as the first step to disarmament and peace. In common with most democratic leaders, I am convinced that, uneasy though the peace may be which the existence of these weapons protects, their disappearance tomorrow would dreadfully increase the dangers of war. With her marked superiority in other forces and arms, the Soviet Union could overrun Europe almost at will, sweep into Africa, and become the terror of the world. Unless disarmament affects all forces and all weapons, it can be a snare and a delusion.

The other task of democratic statesmen is to continue their efforts to persuade the communist powers that, if the power of destruction on the great scale has become mutual and overwhelming, it is high time that the immense possibilities of applied science should be increasingly diverted to the peaceful service of ordinary men and women.

These are important considerations. But my real purpose tonight is to invite you to consider how far these remarkable events are calculated to distort our own standards of civilization. In other words, I want, so far as I can, to recall everybody to an attitude of balanced judgement. For the truth is that in my own lifetime scientists have wrought miracles, some of which operate entirely in the direction of preserving and enlarging human life, and some of which, as they are now regarded, are designed to create a new and horrible capacity for the destruction of human life. Scientists are not alone to blame for this. They have tackled their problems and pursued their search for scientific truth. If other men, speaking on behalf of their nations of people, care to use these great discoveries for evil, that, say the scientists, is not the responsibility of the research worker. This is, I think, not entirely true. "Hath not the potter power over the clay, of the same lump to make one vessel unto honour, and another unto dishonour?" Scientists are not a race apart. They are citizens, bound to a social consciousness and social duties. They cannot, any more than non-scientists, stand aloof from the great moral issues. If it be true, and it certainly is, that the liberty of the modern scientist to pursue his chosen study is part of that great structure of self-governing and self-disciplined freedom which the institutions of the democratic world have painfully but persistently developed, the scientist has a special interest and a share of duty to maintain the structure. Liberty is under challenge. Even in some of its historic homes in Europe it has been beaten with blood into the ground. We are all bound to face these facts. As Bacon said, "It is a strange desire to seek power and to lose liberty." This does not mean that our scientists are to be afraid to toil and to discover and to make known. But it does mean, as a very able man wrote to me recently, that "as science breeds power to alter the shape of continents and the destiny of myriads of human beings, it must engender within its ranks a sense of responsibility comparable to its sense of scientific discipline". Putting this in my own way, science may well fashion the amoral instrument, but scientists, speaking and acting with superior special knowledge, must use all their influence to see that the instrument is used to serve the ends of individual freedom and public virtue. The scientist is not to forget that natural philosophy cannot make its best contribution to life unless it is accompanied by a moral and mental philosophy which will give it balance.

The formulation and expression of a social consciousness; the recognition in this consciousness of the paramount need for the preservation of the spirit and institutions of freedom; these are among the greatest duties we all owe to civilization. If every specialist were to contract out of these

duties and leave them to others, the result would be calamitous.

I am prepared to assert that the dreadful rise of Hitler was in no small measure due to the fact that Germans, highly trained to think in special disciplines, had been too much and too long content to leave matters outside those disciplines to the unguided decision of the incompetent or the unscrupulous.

Charles Morgan had a passage in his remarkable book, "Liberties of the Mind", which I adapt to my present theme:

> It is necessarily hard for any man to know when he is surrendering a part of the liberties of his mind. He can recognise constraint upon his actions or upon that expression of opinion which is itself an action, but there is for him no self-criticism more difficult than the recognising that within the house of his mind, in which he believes himself to move freely, certain rooms are locked *of which he has surrendered the keys.*

It seems to me that in these matters we have, momentarily as I hope, been tempted to meet our potential enemy on his own ground. He says in effect: "Why do you people in the western world worry about your outmoded systems of free government and enterprise? Why, we under our system have become the greatest scientific people in the world!" Similarly, by implication and by moving signs in the sky, he is saying to the numerous new nations, particularly of Asia, the uncommitted nations, the nations entering into self-government and anxious to establish guiding posts for the future: "Why should you be misled into following the worn-out democratic ideas? What you need is science. We are the people who can give it to you. It is our system of government which can produce it most effectively." And so Sputniks are projected into space, and hundreds of millions of people gaze at them travelling across the sky and are tempted to bow down and worship them.

Yet what are the facts, put into the scales, brought to the balance? The facts are that in the field of research for the benefit of mankind, the free peoples have in our own time a record beside which the record of the enslaved nations of communism pales into insignificance. It is, I believe, high time that we began to explain to the new nations of the world the significance of these matters.

I am not a scientist, and therefore I cannot speak as one. I will therefore confine myself to those matters which are widely known among normally educated people.

Recently a friend of mine offered, in my presence, the view that many hundreds of millions of people will be more susceptible to the terror that flies by night, to the demonstration of power and the threat contained in Sputnik, than to those matters which, so far from threatening their lives, promise to extend and enrich them. For all I know he may, in the short run, be right. But the fate of mankind will be sealed if we take only short views. If we are to advance civilization, we must take long views and must make it clear to all other people that the long view is the one which will, in the end, bring to them and their descendants happiness and peace.

Civilization connotes balance. Effort will soon exhaust itself without relaxation. Grave matters are best judged in an atmosphere of occasional hilarity. In England, during the grim early months of 1941, nothing gave such assurance of ultimate victory as the rich and defiant humour of those who lived and worked in the middle of destruction. It is this instinctive sense of balance which saves civilized nations from crazy fanaticism; which makes their occasional hatreds so short-lived; which induces them to "live and let live"; which is, even in the moment of conflict, the only sure hope of ultimate peace and understanding.

Balance of this kind is constantly threatened by sudden reactions, natural or "whipped-up", to unexpected and spectacular achievement elsewhere. The Sputniks represent a great success for the Soviet Union in a field to which they have directed a great deal of skill and effort. It would be foolish to underestimate that skill and effort. But it would be even more foolish to treat it as a proof of our inferiority in the world of science or the much more important world of civilization.

What are our reactions to the Sputniks to be?

The quick answer is: "We must produce more and better scientists." This is, beyond doubt, true. But scientists for what? That is the crucial question. God forbid that we should concentrate our efforts upon applying science to purposes of terror or destruction to the exclusion of science for the development of resources and the betterment of mankind.

I recently discussed this matter with a very distinguished research scientist of the Australian National University, Professor Ennor, who, like myself, is concerned at the recent threats to our sense of perspective. I asked him whether I was, as a layman, right or wrong in thinking that, in the over-all consideration of the achievement of modern science, the western world could claim a preponderance of constructive and useful achievement, and that, despite the inevitable demands of defence, we should not let down our efforts in the constructive field. Speaking with great scientific authority, he said that I was right. He has put himself, very generously, to the trouble of giving me some outstanding illustrations to support this view.

Even in the world of atomic physics the great basic discoveries have occurred in Great Britain and the United States. But the advances in medical research have almost eclipsed those in physics. We have already come to regard many of them as commonplace. Yet they have meant that in this century the expectation of life has been increased, in western countries, by probably 15 years. Professor Ennor has given me examples in the field of biochemistry.

Insulin, which has revolutionized the lives of millions of diabetics, arose from initial work by two German scientists. The first active preparation was made by Canadians. It was isolated in a pure state by an American.

The discovery and application of the various vitamins covers a history in which scientists in Great Britain, the United States, Switzerland, Holland and Denmark occupy pride of place. The "sulpha" drugs and antibiotics, those new and valiant friends of man, take us back to a German scientist as recently as 22 years ago, and to British scientists a few years later. Modern chemotherapy thus began. In 1941 came the isolation of penicillin at Oxford—a remarkable achievement with which an Australian name, that of Howard Florey, will always be honourably associated.

We think today of nuclear research too exclusively in terms of fissionable material for bombs. But the use of radioactive isotopes in biochemistry derives from a Swedish scientist only 34 years ago, and has been marked by astonishing development in the United States and in Great Britain.

These few examples serve to remind us that in the great story of scientific achievement, democracy need not make a regulated bow in the direction of communism.

But my theme goes beyond this. Such facts as those I have mentioned effectively disprove any suggestion that the Russians possess some superior scientific genius. It concedes that in one highly specialized department the Russians may, temporarily at least, have outstripped us. As this is not the simple result of superior scientific intelligence, it must be due to the capacity of the Soviet Union to select and train scientists and technologists, and to order scientific labour into appointed tasks. In the result, government determines both the programme of research and the activities of the research workers. If it decides that, in a bid for the world domination of materialistic communism, it will subordinate other scientific activity to the production of instruments of terror, so that terror may succeed where guile has failed, it has no free electors or enlightened citizens to restrain it. Its scientists may persuade themselves that they enjoy freedom in their own field. But it is a freedom hemmed in by slavery.

Once we recognize these facts we will see that, in some current clamour on our side, there is a danger that we may be urged to adopt the Russian method in order to achieve the Russian result. Let us constantly remember that scientific defence provision is, for us, solely a means of preserving democratic freedom and civilized individual rights. It would be the ultimate tragedy to abandon the purpose of defence in order to prepare as the potential

enemy prepares. In actual war we put many particular freedoms in pawn so as to preserve the great freedom. But such a process should not long survive when war has been won. *A fortiori*, it should not become an established feature of what may well be a prolonged period of uneasy peace. If provision for military scientific research and development comes to be regarded not as a free national effort but as something requiring the abandonment of freedom and the acceptance of authoritarian control, we shall have abandoned the case against communism in the very course of making ourselves ready to maintain it.

But I should like to carry this examination further. Nobody will deny that, with the rising pressures of growing populations, with the urgent need to discover and unlock new resources, the place of the scientist in modern society must be one of growing importance. My own government, by the far-reaching and costly university decisions which I recently had the pleasure of announcing to Parliament, has recognized this. Without more and more scientists and more and more scientific research, the material future of our people cannot be assured and enlarged.

But the housing and feeding and clothing and curing of mankind, though vital and imperative, are not an end in themselves. They are the means to a great end; when "body gets its sop, and holds its noise, and leaves soul free a little".

It is, indeed, this confusing of means with ends that has bedevilled the twentieth century. It is grimly significant that the century which has seen the greatest scientific achievements of recorded history has been, perhaps more than any other, disfigured, not only by wars of a stupendous range and intensity and destruction, but by widespread attacks upon the religion of love by organized hatreds and cruelties of the most barbarous kind. Humane studies have faltered, not only before active opposition, but in the face of impatience and indifference. Values have become debased or obscured. There is a widespread clash of selfish interests. The foolish slogan of "something for nothing", which leaves Lloyd George's famous "ninepence for fourpence" far behind, has a false currency. And the grim law of Gresham has seen the false currency driving out the good. The second World War was thought likely to usher in a new era of internationalism. It has, in fact, led to a new wave of acute nationalism, frequently marred by racial bitterness, and accompanied by a new communist imperialism all the more sinister because it professes to be the foe of imperialism.

Hitler is defeated and dead, but his harsh theories of racial superiority have left many converts. Mussolini is overthrown and dead, but his irredentist fancies are flourishing elsewhere.

It is not sufficient to say that there are brighter colours in the picture; that more people than ever before desire peace and are working for it; that the scientists have created the means for increased human health and happiness; that immense social progress has been made. These things are splendidly true, and I have said a great deal about them. But they will not ultimately dominate and redeem the history of this century unless we positively strive to get rid of those basic errors which have produced or permitted the evils which I have attempted to describe.

As an instrument, science can achieve either good or ill. That will depend upon the minds and spirits of those who use the instrument. Our natural and acquired capacity for extravagance, skilfully played upon by the sensationalists of the fleeting day, can too easily lead us to believe that the need for more scientists is such that all other higher studies should be subordinate; that the study of physical nature is the only thing that greatly matters; that if knowledge comes, wisdom will not linger. Believing as I do that science and wisdom have no necessary connexion, and that scientific study and achievement are not ends but means, I am driven to the conclusion that what the scientists do or will do will put into our hands discoveries which can be the means of destruction or of a new and complicated form of technological slavery, but which, wisely used, can be the means of human salvation. The answer will depend upon our character, our broad intelligence, and our wise and understanding judgement.

I invite you to remember with pride that it was in the free world that the two great institutions of liberty, Parliamentary self-government and the rule of honestly administered law, were fashioned. They have made a mark on this century compared to which a Sputnik is unimportant. It is too frequently forgotten, and sometimes by countries which should remember it, that, if Great Britain has not as yet fired a satellite into space, she has, by a creative modern policy, converted colonies into independent nations, founded upon parliamentary sovereignty and enriched by the rule of law, while the Soviet Union has been busy converting independent nations into colonies under the rule not of law, but of the tank and the bomb. The enslavement of Poland and East Germany and Czecho-Slovakia and Hungary stands in stark contradiction to the enfranchisement of India, Pakistan, Burma, Ceylon, Ghana, Malaya, the West Indies.

But if some of these great and revolutionary achievements seem to some of us to be so commonplace as to be outdone by Sputnik, let us be good, sound, practical, technological fellows together, and consent to be judged in the field of science, pure and applied. The great pure scientists, from Bacon to Newton to Rutherford, did their work in the atmosphere of intellectual liberation. If living today, they would have no headlines. Their great mental powers were wedded to almost inhuman patience. They had no clients clamouring for results. Today we are "practical" men. We want results, and we want them quickly. This urgency of demand, since it cannot sensibly be applied to pure or basic scientific research without great harm, has tended to concentrate itself upon applied science, thus paradoxically (as I hope) speeding up pure research by the simple and unconscious expedient of leaving it uninterrupted!

The results, in the free world, have been phenomenal. Whatever the potentialities of space missiles for destruction, they are as nothing when compared with what has already been done for construction; for the combating of disease and the prolongation of life; for the development of natural resources; for the improvement of public health and sanitation; for the encouragement of literacy; for the fluid movement of people and of goods; for the raising of material standards of living. We have become so adept at demanding (and frequently obtaining) something new and better next year that we sometimes forget that the average man today in Australia (to take a near example) enjoys as a matter of commonplace right privileges and amenities which for his grandfather represented either the unknown or the vaguely hoped for.

Nothing that I say or have said tonight is to be regarded as a plea for complacency. The work to be done always exceeds the work already done. Vigour is essential. But all our efforts can be wasted if we lack a sense of direction and purpose. I, for one, am far more afraid of the impact of Sputnik upon our minds that I am of its threat to our physical existence. For the truth is that the nearer the world comes to saturation point in its brilliantly acquired capacity for mutual destruction, the more certain it becomes that another global war would return what remained of mankind to the dark ages; the more evident it is that such a war can be initiated only by insanity or by blundering accident. Protection against war therefore involves two elements.

The first element is complete readiness on the part of the free world, the non-aggressive world. It must, not from choice but from necessity, maintain such a degree of defensive and counter-attacking power as will deter aggression. This involves grievous burdens, but they must be borne.

The second element is no less important. Indeed, it is vital. It is that our social policies, and particularly educational policies, should be so devised as to encourage sanity and responsibility and discourage blundering accident. Psychologically, the true answer to the threat of war is to be found in the improving nature of man himself. Whatever we are called to do in the field of new and better satellites and ballistic weapons, we must not forget that the true function of science is to enlarge the boundaries of human knowledge, and that of applied science to raise the standards of human living and happiness. Moreover, we cannot all be scientists; it would be a black day for the world if we were. We need more medical skill; more

miracles from the laboratories of the biochemists; more labour-saving devices in homes; cheaper and more efficient methods of construction. But these are not an end in themselves. The true end to be served is the enlargement of the human mind and spirit. We have tended to lose sight of this great truth. Our mechanical skill has tended to overthrow our sense of values. We find in television a substitute for reading, and in the wireless a substitute for thought. We drive in handsome and powerful motor-cars in long and melancholy procession on crowded highways at week-ends, inhaling fumes and wondering vaguely how long the return journey will take. In those far-off ridiculous days when the higher education was classical and humane, when men stored up in their minds a love of knowledge of letters and philosophy and history, our fathers had not reached this strange state of worship for the machine and obedience to its demands.

If we look at the matter in this way we see science in its proper perspective; not as the master, but as the servant. We are not to adopt the Shorter Catechism to read: "The chief end of man is to glorify science and enjoy it for ever."

As we look forward, therefore, we are not to allow our education of new generations to be distorted. More scientists; more scholars; more scholarly scientists; more scientific scholars; more historians and philosophers and poets. For if science is truly to serve the cause of civilization it will be because the people to use the advances of science have grown to use them in a civilized way.

With your tolerant consent, I quote from my own recent speech on the universities: "Let us have more scientists, and more humanists. Let the scientists be touched and informed by the humanities. Let the humanists be touched and informed by science, so that they may not be lost in abstractions derived from outdated knowledge of circumstances."

"All things work together for good", it was once said in another context. Yet all good things can be and frequently are used badly. Not all the most brilliant successes in laboratories and factories and fields will make a nation great in the eye of history if it has failed to enthrone the human spirit and to set about it knowledge, and justice, and patience and understanding.

## BORNHOLM DISEASE IN AN ADELAIDE SUBURBAN AREA.

By L. KAUPMEES AND R. A. A. PELLEW,
*Adelaide.*

AN outbreak of Bornholm disease in a circumscribed area in an Adelaide suburb has been studied. As the outbreak showed one or two unusual clinical and epidemiological features, we considered that it was worthy of being reported. In addition, virus studies were carried out and are reported in the accompanying paper (Duxbury and Warner, 1958). Altogether we saw 23 patients.

The outbreak occurred in a new housing area in the practice of one of us. It was of great interest that all the patients lived in homes surrounding two shopping areas. We did not find any cases in a zone immediately surrounding our group, which suggested that this epidemic was localized.

### Symptoms and Signs.

In the series of 23 patients the outstanding symptoms were as follows: (i) Intense headache of insidious onset. The headache was usually of a bursting nature, occipital or frontal or both, and remained constant for five days or more. (ii) A low-grade fever, the temperature rising to 100° F. in the evening. The fever usually lasted from five to seven days, but of interest was the sustained fever in five cases. In these there was a persistent elevation of temperature from 99° to 99·8° F. for as long a period as six weeks, and in fact in one case such fever was present for three months. (iii) Stiffness in the back of the neck accompanied by much muscle pain. All patients complained of this. (iv) Muscle pain. This was experienced consistently also along the attachment of the diaphragm on both side, more anteriorly than posteriorly. Other sites of pain were the upper part of the trapezius and, peculiarly, a triangular area in the *quadriceps femoris* in the front of the thigh. All patients complained of pain in the orbit when the eyes were moved from side to side. We considered this to arise from the extrinsic eye muscles. There was much less consistent pain in other parts of the body, such a the upper part of the arm and the calf. (v) Nausea, vomiting and constipation. These were common, and vertigo occurred in every case.

There were no physical signs of note, except tenderness under both costal margins and neck stiffness. A pleural friction rub was not discovered in any case.

The severe upper abdominal pain and tenderness in a few cases simulated an "acute abdomen", but on further questioning of the patients, the pain on eye movement, headache and pain in the front of the thigh were sufficient to exclude the diagnosis of an "acute abdomen", and we considered these symptoms were sufficient to warrant a diagnosis of Bornholm disease.

A typical case is described in more detail.

The virus was isolated from the stools of this patient (Duxbury and Warner 1958). He was a healthy man, aged 23 years, who complained when first examined of pain in the right upper quadrant of the abdomen and in the right quadriceps, vertigo, a "splitting" headache, stiffness of the neck and nausea. Examination of the patient showed him to have a temperature of 99·8° F., acute tenderness under both costal margins and a stiff neck. This episode was short-lived and he was free of symptoms within a week. However, about six weeks later he had a relapse of symptoms, which were very much the same as in the initial attack, and they again lasted about one week.

In most cases the disease was of short duration in the acute stage, but in a few relapse occurred. In some patients there were pronounced psychological sequelæ; depression was profound; patients complained of irritability, lack of concentration and sudden changes of mood. The morbidity was such that some of the patients were confined to their homes for periods as long as three months.

The majority of patients were young adults, unlike those in the epidemic described by Warin *et alii* (1953), in which the greatest incidence was between the ages of five and fifteen years. In our epidemic there was no incident of more than one clinical case in any household (contrast Warin *et alii*, 1953).

We performed no lumbar punctures. Virus investigations were carried out in all 23 cases. The diagnosis was confirmed in one of our cases by isolation of the virus Coxsackie B2 and by the establishment of rising titres of antibodies (Duxbury and Warner, 1958).

### Treatment.

The treatment carried out consisted of bed rest and the treatment of symptoms. We found the patients obtained great relief from the unpleasant vertigo when given "Dramamine" derivatives, often combined with pyridoxine. The tranquillizing drugs relieved the depression. The treatment of the patients with short-lived illness was simple, but those with sustained pyrexia presented a greater problem. It is very difficult to continue to reassure a depressed patient who sustains an elevation of temperature in the evening. One of us has been confronted with this problem of continued fever in the management of other virus diseases such as glandular fever, and in a disease resembling poliomyelitis, and has used intravenous injections of arsenic with some good effect in several cases. Apropos of this, the case history of one of our patients is presented in more detail.

A woman, aged 43 years, first reported in April, 1957, with the history of a slight fever (temperature 99·4° F.) every evening for the preceding five days. She complained of quite severe frontal headache, nausea, vertigo, and pain along the attachment of the diaphragm and in front of the thighs. The low-grade fever persisted, as did the pains and malaise till July, when it was decided that some arsenic by intravenous injection should be tried. Four injections of "Novarsenobillon" were given twice weekly in the dose of 0·3

gramme, 0·45 gramme, 0·6 gramme and 0·75 gramme. At the end of a fortnight her fever had subsided and her pains had disappeared, and, within the next week, she reported that she was feeling well. She has remained well since, and has returned to her occupation.

We can offer no explanation of this gratifying result, but it appears to us that the efficacy of arsenic in this and other such cases is perhaps more than coincidence. However, we admit that the disease process may well have burned itself out at this stage without the use of arsenic.

Ten of our patients were carefully observed later, and no residual muscle weakness was detected. It was not considered necessary to look for muscle weakness in the other 13 patients.

The interesting feature of the epidemiology in our series was that the cases occurred in a localized area surrounding two shopping centres in the suburb.

### Summary.

We must stress that we were impressed by the constancy of the headache, which in most cases was not overshadowed by the chest pain (cf. Warin *et alii*). The pain in the front of the thigh was real. We draw attention to the sustained fever, which was also recorded in the Oxford epidemic, and also to the ensuing psychological symptoms.

### Conclusion.

An epidemic of Bornholm disease has been described. In many ways the symptomatology was typical, but emphasis is laid upon the persistent headache, pain in front of the thigh and pain on eye movement. Persisting fever was noted in some cases; in one such case intravenous injections of arsenic were given and the patient recovered after the fourth injection.

### Acknowledgements.

Our thanks are due to the members of the Medical Research Division of the Institute of Medical and Veterinary Science of South Australia for their cooperation.

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## EPIDEMIOLOGICAL AND LABORATORY INVESTIGATIONS ON BORNHOLM DISEASE IN ADELAIDE, 1957.

By A. E. Duxbury and Peter Warner.[1]

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In April, 1957, our attention was drawn to an outbreak of Bornholm disease which is described in the accompanying paper (Kaupmees and Pellew, 1958), occurring in a localized area in the suburbs of Adelaide.

Since it has been shown that certain members of the Coxsackie group B viruses are associated with this disease (Weller, Enders, Buckingham and Finn, 1950; Dalldorf, 1955) and with a proportion of cases of aseptic or benign meningitis (Curnen, Shaw and Melnick, 1949; Rhodes and Beale, 1957), we were asked to carry out laboratory investigations on the patients comprising the above-mentioned outbreak.

It seemed to us that the outbreak had unusual features in addition to its apparent circumscription. Consequently we traced 30 additional cases of epidemic myalgia and two of benign meningitis which were attributed to the Coxsackie virus.

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This paper describes certain epidemiological observations made on Kaupmees and Pellew's patients and on our own patients, and the isolation of a strain of Coxsackie B2 virus from a case of Bornholm disease. Although it is known that this type of Coxsackie virus is associated with aseptic meningitis, this is the first report of the association of type B2 with Bornholm disease. Strains of the same virus were isolated from the patients with benign meningitis.

Other laboratory investigations carried out in an attempt to afford diagnostic facilities to clinicians are described. These were not conspicuously successful but, for this reason, were thought worth reporting and discussing.

### Materials and Methods.

#### Source and Collection of Specimens.

After Kaupmees and Pellew had satisfied themselves that they were dealing with an outbreak of Bornholm disease, we were informed immediately of the occurrence of new cases. Blood was obtained, usually by one of us, as soon as possible after the onset of the disease. After clotting had occurred, serum was separated and stored in the frozen state. If this was not immediately possible, the whole blood was kept at a temperature of 4° C. However, in all cases serum was separated and frozen within 48 hours of its having been taken from a patient.

Fæces were obtained as early as possible in the disease, and were brought to the laboratory, usually within a few hours, certainly within 24 hours of having been passed. They were stored at a temperature of −70° C. until examined.

About the beginning of May, 1957, publicity in the newspapers and on the radio was given to the outbreak described by Kaupmees and Pellew (1958). Also, through the courtesy of the South Australian Branch of the British Medical Association, its members were informed of our interest in investigating cases of suspected Bornholm disease. In these ways some 30 patients were brought to our attention. Our purpose in collecting these patients was primarily for epidemiological and laboratory investigation. They were not followed clinically in the same detail as those of Kaupmees and Pellew (1958). However, all of them were interviewed by one of us (A.E.D.). Patients chosen for investigation were those with muscular pains as the prominent feature of the illness, often associated with one or more of the following: headache, fever, vomiting, anorexia, nausea, sore throat and relapses. The distribution of these signs and symptoms is shown in Table I. Other features of the illness occasionally included hip pain, shivering, delirium, dizziness, enlargement of lymph nodes, cough and lassitude. When possible, specimens of blood and fæces were obtained from the patients and were treated in the way we have already described.

Two patients with benign meningitis, originally thought to be suffering from non-paralytic poliomyelitis, were investigated in addition to those with epidemic myalgia. Agents, cytopathogenic for monkey kidney tissue culture, were isolated from the fæces of these patients during the course of poliomyelitis investigations. As will be shown, these agents were almost certainly identical with the Coxsackie B2 virus isolated from one of Kaupmees and Pellew's patients.

#### Preparation of Fæcal Extracts.

Fæces were removed from storage and allowed to thaw at room temperature. About two grammes were shaken vigorously for three minutes with 10 millilitres of either maintenance medium (see under "Tissue Culture") or 10% rabbit serum saline containing, in each case, penicillin and streptomycin (1000 units and 1000 milligrammes per millilitre respectively). The emulsion was centrifuged at about 3000 revolutions per minute for 30 minutes, and the upper half of the supernatant fluid was removed as "fæcal extract" for further investigation; the remainder was discarded. The fæcal extract was allowed to stand at room temperature for one hour (the usual method for tissue culture) or at a temperature of 4° C. overnight (the usual method for animal inoculation).

TABLE I.

*Signs and Symptoms in 30 Cases of Bornholm Disease, Adelaide, 1957.*

| Muscular Pains. | Total. | Other Muscular Pains. | | | | Other Signs and Symptoms. | | | | | Relapses. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Neck. | Shoulder. | Limbs. | Back. | Fever. | Headache. | Vomiting. | Sore Throat. | Anorexia and Nausea. | |
| Chest only .. .. | 23 | 2 | 8 | 9 | 8 | 12 | 10 | 6 | 3 | 8 | 5 |
| Abdomen only .. .. | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 0 | 1 | 2 | 4 |
| Chest and abdomen .. | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
| Neither chest nor abdomen | 4 | 4 | 2 | 1 | 1 | 0 | 4 | 1 | 3 | 0 | 1 |
| Total .. .. | 30 | 8 | 12 | 13 | 10 | 13 | 17 | 7 | 7 | 11 | 11 |

### Animal Inoculation.

Infant mice of the Institute strain less than 30 hours old were used for inoculation. For attempts at isolation at least two litters of mice were used (average litter size six to seven mice). Fæcal extract was inoculated intraperitoneally in 0·5 millilitre amounts. The mice were observed daily for signs of illness or death for 21 days or more.

### Tissue Culture.

Tissue cultures were prepared by the continuous trypsinization of fragments of monkey kidney according to the method of Rappaport (1956). To each test tube 9/16 inch in diameter was added 0·5 millilitre of growth medium containing $3 \times 10^5$ to $5 \times 10^5$ monkey kidney cells. The growth medium was 0·25% lactalbumin hydrolysate and 5% calf serum in Hank's salt solution with phenol red (0·002%), penicillin (100 units per millilitre) and streptomycin (100 milligrammes per millilitre). Rubber stoppers were fitted to the tubes, which were then incubated for four to five days, after which time a sheet of cells formed, suitable for the recognition of virus growth.

For attempts at isolation growth medium was removed and each fæcal extract was inoculated in two different ways, as follows:

(*a*) To each of two tubes 0·5 millilitre of fæcal extract was added, and allowed to stand in contact with the tissue culture for two hours. Afterwards the fæcal extracts were removed and the cultures washed three times with buffered saline. Maintenance medium (0·25% lactalbumin hydrolysate and 2% calf serum in Earle's salt solution with phenol red and antibiotics as for the growth medium) in 1·0 millilitre quantities was added to each tube, which was then placed on its side and incubated at a temperature of 37° C. (*b*) To each of two tubes was added 1·0 millilitre of a 1:10 dilution of fæcal extract in maintenance medium. The tubes were incubated as in (*a*).

The four tubes used for each fæcal extract were examined under the low power of the microscope for cytopathogenic effects after one, two, four, six and eight days' incubation.

### Neutralization Tests.

Both serum and virus dilution methods were used in neutralization tests. Mice used were infant mice less than 30 hours old at the time of inoculation, and at least four litters were pooled and redistributed among an appropriate number of mothers. The virus preparation consisted of an extract of suckling mouse carcasses from the second, fifth and six intraperitoneal passages of the Kaiser strain (described below) of the Coxsackie B2 virus. The negative logarithms of titres, by the method of Karber (Finney, 1952), were 5·2, 6·6 and 6·3 respectively.

#### *Serum Dilution Neutralization Test.*

The serum dilution test was performed as follows:

Serum was diluted 1:5, 1:50 and 1:500 in saline, and a volume of each dilution was mixed with an equal volume of a dilution of virus suspension. Hence the final serum dilutions were 1:10, 1:100 and 1:1000. The serum virus mixture was incubated at a temperature of 37° C. for one half to one hour and then inoculated intraperitoneally into suckling mice, which were observed for 21 days for signs of characteristic illness and death. Those deaths occurring within the first 48 hours were disregarded. A control was set up in parallel in which normal rabbit serum was used in place of the patient's serum.

#### *Virus Dilution Neutralization Tests.*

Virus dilution neutralization tests were carried out as follows:

Equal volumes of undiluted serum were mixed with each of three dilutions of fifth and sixth passage virus material. Tenfold dilutions of virus material were used; initially these dilutions ranged from $10^{-4}$ to $10^{-6}$, but when it was seen that death did not occur invariably in the highest, they ranged from $10^{-3}$ to $10^{-5}$. The virus-serum mixtures were incubated and inoculated in the same way as we have described for serum dilution neutralization tests.

Interpretation of the neutralization test results presented some difficulty, since mice frequently died from non-specific causes, particularly in the first two days after inoculation. On several occasions it was necessary to repeat tests to obtain a reasonable comparison between test and control groups. Consequently, no attempt was made to attach a numerical value to the neutralizing activity of a serum.

## RESULTS.

### Epidemiological Findings.

Table II shows the geographical distribution of cases of Bornholm disease occurring in the Adelaide suburbs, including those described by Kaupmees and Pellew (1958). It will be seen that cases occurred in most geographical districts encircling metropolitan Adelaide, and not only in one suburb. The number of cases discovered is too small to indicate marked prevalence of the disease in any one area. In this connexion it should be remembered that Kaupmees and Pellew's cases were collected over a period of nearly a year, whereas the others were collected during about half that time. Also, radio and newspaper publicity drew attention to the occurrence of the disease in the area. This may have caused patients with mild disease to seek advice when, in the absence of publicity, they might not have done so.

Table III shows the age and sex distribution of the patients suffering from Bornholm disease. The noteworthy points are that there is a preponderance of females, and that the ages of three-quarters of the patients lay between 20 and 54 years. In this range the numbers of patients in each five-year age group were approximately the same.

Figure I, which includes the two patients who contracted aseptic meningitis, shows the monthly incidence of Bornholm disease, and it is seen that cases were detected throughout the year even in the circumscribed area described by Kaupmees and Pellew (1958). In fact, at the present time cases are still being brought to our attention. Thus, there is no evidence of an outbreak limited in time with the characteristic peak of an explosive outbreak. Consequently, we cannot draw conclusions concerning the seasonal incidence of the disease.

### Virus Isolation.

#### *The Kaiser Virus.*

A virus was isolated by the inoculation of suckling mice from fæces obtained seven days after the onset of illness (in May) in a case described by Kaupmees and Pellew

(1958). In the first passage mice became ill on the eighth and tenth days after inoculation; the most remarkable feature of their illness was hind-limb paralysis. In the second and third passages the incubation period shortened to four to six days, and the characteristic features of illness were failure to thrive, hind-limb or total paralysis and cyanosis, often followed in a day or two by death. By the sixth passage death of the mice often occurred without the observation of prior illness, and all mice died between the second and fourth days. The virus was also isolated in monkey kidney tissue culture at the same time.

Table II.

*Geographical Distribution of Cases of Bornholm Disease, Adelaide, 1957.*

| Region. | Number of Cases. |
|---|---|
| South-west: | |
| Kaupmees and Pellew (1958) .. | 23 |
| Others .. .. .. .. .. | 6 |
| South .. .. .. .. .. | 4[1] |
| East .. .. .. .. .. | 9[1] |
| North-east .. .. .. .. .. | 2 |
| North .. .. .. .. .. | 10 |
| North-west .. .. .. .. .. | 1 |
| Total .. .. .. .. | 55 |

[1] Includes one case of aseptic meningitis.

Neutralization tests with the patient's own acute and convalescent serum showed a rising titre of neutralizing antibodies against the virus. Table IV shows the results. All four mice in the control group died, whereas in the first test serum group there were a few survivors, and in the groups with the two lower dilutions their survival time was prolonged in comparison with the control group. In the second serum group all mice with the highest dilution survived, and all but one of those with the lower two dilutions, in which also no paralysis was observed.

Table III.

*Age and Sex Distribution of Patients with Bornholm Disease, Adelaide, 1957.*

| Age Group. (Years.) | Patients. | | |
|---|---|---|---|
| | Male. | Female. | Total. |
| 0 to 14 .. | 5 | 3 | 8[1] |
| 15 to 19 .. | 0 | 1 | 1 |
| 20 to 24 .. | 2 | 1 | 3 |
| 25 to 29 .. | 3 | 7 | 10 |
| 30 to 34 .. | 1 | 6 | 7 |
| 35 to 39 .. | 2 | 4 | 6 |
| 40 to 44 .. | 0 | 6 | 6 |
| 45 to 49 .. | 3 | 2 | 5 |
| 50 to 54 .. | 1 | 3 | 4 |
| 55 to 79 .. | 2 | 3 | 5 |
| Total .. | 19 | 36 | 55 |

[1] Includes one male and one female patient with aseptic meningitis.

The virus was identified for us by Dr. D. McLean, of the Commonwealth Serum Laboratories, as a Coxsackie B virus, type 2.

### *Viruses from Patients with Benign Meningitis.*

Viruses isolated in monkey kidney tissue culture from two patients with aseptic meningitis during the course of poliomyelitis investigations were neutralized (Table V) by an antiserum prepared again the Kaiser virus in adult mice immunized by intraperitoneal inoculations of seventh passage material (0·5, 1·0, 1·5 and 2·0 millilitres given at weekly intervals, followed by bleeding a week later). One of these patients came from the southern perimeter of Adelaide and the other from the northern perimeter.

### Attempted Virus Isolations.

Attempts were made to isolate viruses from the fæces of an additional 21 patients with Bornholm disease. The fæces had been obtained more than 14 days after the onset of the disease on two occasions—from eight to 14 days after on 11 occasions, and less than seven days after on eight occasions. A few early attempts included the subcutaneous and intracerebral inoculation of suckling mice in addition to intraperitoneal inoculation. Up to four blind passages were attempted with several specimens of fæces. Thirteen specimens of fæces obtained from two to nine days after the onset of the disease and tested in suckling mice were also tested in monkey kidney tissue culture. Four of these were taken up to four blind passages and the remainder were tested with one passage only. In addition, two specimens of fæces obtained five and three days after the onset of disease were tested in monkey kidney tissue culture only.

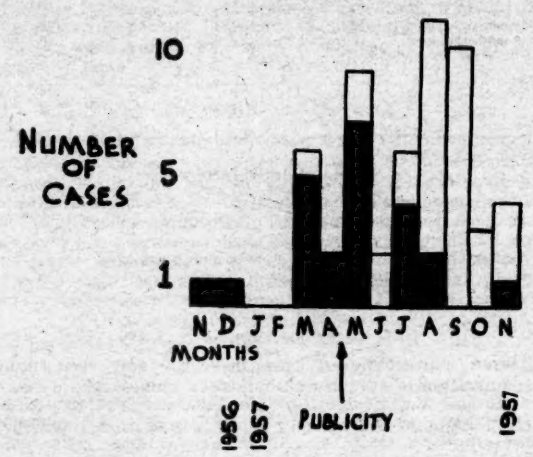


Figure I.

Monthly incidence of Bornholm disease, Adelaide, 1956-1957. Solid columns, Kaupmees and Pellew's cases (1958); open columns, our own cases.

Table IV.

*Demonstration of Rising Antibody Titre in Kaiser Serum against His Own Virus.*

| Serum. | Logarithm of Serum Dilution. | Survival Period and Paralysis.[1] | Mortality.[2] |
|---|---|---|---|
| First specimen .. | −1 | 14*, 8*, 8 | 1/3 |
| | −2 | 10*, 11*, 25*, 8* | 3/4 |
| | −3 | 5*, 6, 6, 7* | 4/4 |
| Second specimen .. | −1 | 8, 8, 8 | 0/3 |
| | −2 | 16, 8, 8 | 1/3 |
| | −3 | 8*, 8*, 8, 8 | 0/4 |
| Control .. .. | −1 | 5, 6, 7, 7* | 4/4 |

[1] The numbers in the "Survival Period and Paralysis" column indicate the time in days after inoculation when death occurred; "8"=survived 21 days; "*" denotes the occurrence of paralysis at some time before death or within 21 days in survivors.

[2] The denominators in the "Mortality" column indicate the number of animals inoculated, and the numerators the number of animals that died; second passage Kaiser virus (negative logarithm of titre 5·2) used in tests at a dilution of 1 : 100.

All attempts at isolations, other than those successful attempts we have mentioned previously, resulted in failure to discover a causative agent. In addition, fæces from eight family contacts of patients obtained from four to 11 days after the onset of illness in the patients failed to yield a virus.

### Neutralization Tests.

Serum from 24 patients, 17 of whom were Kaupmees and Pellew's patients, was tested for neutralizing antibodies. A total of 13 specimens had some neutralizing activity against the Kaiser virus.

TABLE V.

*Neutralization of "Parsons" and "Germein" Viruses by Kaiser Virus Mouse Antiserum.*

| Logarithm of Virus Dilution. | "Parsons" Virus.[1] | | "Germein" Virus.[1] | |
|---|---|---|---|---|
| | Control. | Test. | Control. | Test. |
| −1 | 4/4 | 5/6 | 7/7 | 5/5 |
| −2 | 2/2 | 2/7 | 7/7 | 5/6 |
| −3 | 6/6 | 2/6 | 7/7 | 2/7 |
| −4 | 3/5 | 1/6 | 7/7 | 3/6 |
| −5 | 1/1 | 1/6 | 4/4 | 1/6 |
| −6 | 4/4 | 0/6 | — | — |
| Total .. | 20/22 | 11/37 | 32/32 | 16/30 |
| Negative logarithm of titre .. | >6·1 | 2·3 | >5·5 | 3·3 |
| Neutralizing index (logarithm) .. | >3·8 | | >2·2 | |

[1] Denominators denote number of animals inoculated, numerators number that died. Both viruses used in third passage. Kaiser mouse antiserum used in a 1:10 dilution (in a 1:10,000 dilution it shows marked neutralizing activity against the homologous virus).

The results of the serum neutralization tests were fairly clear cut, and are recorded in Table VI as the pooled results obtained from testing acute and convalescent sera, between which no observable difference existed. Table VII shows the results of the virus neutralization tests and is

TABLE VI.

*Serum Dilution Neutralization Tests in Cases of Bornholm Disease, Adelaide, 1957.*

| Case Number. | Dilutions of Patients' Serum.[1] | | | Control Serum.[1] 1:10 |
|---|---|---|---|---|
| | 1:10 | 1:100 | 1:1000 | |
| I | 1/9 | 4/11 | 14/14 | 7/7 |
| II | 2/10 | 2/11 | 8/9 | 7/7 |
| III | 0/9 | 6/11 | 11/11 | 5/5 |
| IV | 0/12 | 2/12 | 12/12 | 5/5 |
| V | 3/14 | 14/14 | 12/12 | 7/7 |
| VI | 1/5 | 0/6 | 1/4 | 5/5 |
| VII | 0/12 | 12/13 | 13/13 | 6/6 |

[1] The denominators denote the number of animals inoculated and the numerators the number that died. Sixth passage Kaiser virus (negative logarithm of titre, 6·3) used at a dilution of 1:10,000 in all except Case II, in which second passage (negative logarithm of titre, 5·2) was used at a dilution of 1:1000. The results in Case VI were obtained with a single specimen of serum. The other results are the pooled results obtained with acute and convalescent serum, which showed no observable difference.

self-explanatory. Table VIII shows the results obtained with a single specimen of the serum of the patient in Case XII; a valid comparison between the test and control groups was obtained only with the 1:10 dilution of serum. However, in the test group, not only were there three survivors, but the survival time of those mice that died was obviously prolonged beyond the survival time for the control group, all of whom died. This indicated to us that neutralizing activity was present in the serum.

With four exceptions, two or three specimens of serum were tested from each patient in whom no antibodies were detected. The serum was obtained from one to 118 days after the onset of the disease, and from each patient a specimen was obtained between two and 12 weeks after the onset. The four exceptions were patients from whom only single specimens of serum were obtained 74, 106, 135 and 225 days after the onset of the disease.

From six patients in whom antibodies were demonstrated, a specimen of serum was taken in the first week of the disease and another specimen was taken more than 14 days after the onset. In only one of these patients was a rising

TABLE VII.

*Virus Dilution Neutralization Tests in Cases of Bornholm Disease, Adelaide 1957.*

| Case Number. | Serum. | Logarithm of Virus Dilution.[1] | | | |
|---|---|---|---|---|---|
| | | −3 | −4 | −5 | −6 |
| VIII | Patient .. | — | 3/6 | 2/5 | 3/6 |
| | Control .. | — | 5/5 | 7/7 | 6/8 |
| IX | Patient .. | — | 2/7 | 0/6 | 0/2 |
| | Control .. | — | 6/6 | 2/4 | 2/6 |
| X | Patient .. | 4/8 | 3/6 | 6/7 | — |
| | Control .. | 4/4 | 2/2 | 5/5 | — |
| XI | Patient .. | 0/3 | 2/10 | 3/10 | — |
| | Control .. | 5/5 | 7/7 | 6/8 | — |

[1] The denominators denote the number of animals inoculated and the numerators the number that died. Kaiser virus passage 5 (negative logarithm of titre, 6·6) was used in Cases VIII, IX and X and passage 6 in Case XI. The final serum dilution in each instance was 1:2.

titre demonstrated. This was the patient (Kaupmees and Pellew, 1958) from whom serum was taken six and sixteen days after the onset of illness and from whom a virus was isolated.

TABLE VIII.

*Neutralization Test in Case XII of Bornholm Disease, Adelaide, 1957.*

| Serum. | Survival Period and Paralysis. (Days.)[1] |
|---|---|
| Control .. .. | 5, 6, 7, 7, 9* |
| Test .. .. | 9*, 13*, 13*, 18*, 19*, 19, 8, 8, 8, 8, |

[1] The numbers indicate the time in days after inoculation when death occurred; "8", survived 21 days; "*" denotes the occurrence of paralysis at some time before death or within 21 days in survivors. The patient's serum was used at a dilution of 1:10; second passage Kaiser virus (negative logarithm of titre, 5·2) was used at a dilution of 1:1000.

### DISCUSSION.

The first point of epidemiological interest which arises from our investigations is that Bornholm disease was not confined to the circumscribed area described by Kaupmees and Pellew (1958), but that cases occurred in most geographical regions of metropolitan Adelaide. The total number of cases collected by Kaupmees and Pellew and by ourselves (we will subsequently refer to this joint group as the "Adelaide cases") were insufficient to indicate whether they occurred in focal groups or were evenly spread throughout the city. In fact, we were unable to detect the distinct areas of high incidence described by Warin, Davies, Sanders and Vizoso (1953) and by Harder (1936), although it is also to be noted that Kaupmees and Pellew found their cases grouped closely around two shopping centres. It is also of interest that Kaupmees and Pellew's patients all resided in a new housing estate. Brown, Liddle and Tobin (1952) describe an outbreak occurring in a new housing estate, and Nichamin (1945) describes an outbreak occurring in a housing project for American war workers.

The period during which cases of Bornholm disease occurred extended over many months (Figure 1). This period differed markedly from the epidemics described by Warin *et alii* (1953) in Oxford, and by Harder (1936) in Cincinnati, where, although cases were detected during a period of four months, the main impact of the epidemic occurred over a period of two months, within which time there was a well-marked peak of incidence. Nichamin's (1945) outbreak occurred over a period of four months. Owing to the method used for collecting cases, there is

nothing in our material which may be taken to suggest a seasonal prevalence for the disease. However, it is certain that the disease is not confined to the warmer months of the year, as previous outbreaks apparently were.

Among the Adelaide patients there is a preponderance of females. Harder (1936) found the sex incidence approximately equal, whereas Warin *et alii* (1953) found a slight preponderance and Nichamin (1945) a more marked preponderance of females.

The most striking feature of the Adelaide patients is their age incidence; three-quarters of them are evenly distributed over the range of 20 to 54 years. All other authors have found that the main incidence of the disease is among children and young adults. In the Oxford epidemic nearly three-quarters (73·9%) of all patients were aged 19 years or younger. Dalldorf (1950) has shown that only 3·6% of a group of 28 people with proven Coxsackie virus infection were aged over 19 years. Hence it seems that, at present, Bornholm disease in Adelaide is not a disease of children and their parents, as was the impression gained in the Oxford epidemic (Warin *et alii*, 1953).

There are several possible explanations for the differing epidemiological features of Bornholm disease in Adelaide at present compared with the features described for other outbreaks. They may be due to differences in the climatic and living conditions of the population at risk. If it is assumed, for the present, that one virus is responsible for current cases of Bornholm disease, it may be that in Adelaide the virus has previously spread and has become endemic in the population, which is now partially immune. Perhaps particular types or strains of those types behave differently from others, or may vary in virulence. The explanation which supposes an endemic virus seems to be the most plausible one, and may account for the possible prominence of the disease in the circumscribed area of a new housing estate, described by Kaupmees and Pellew (1958), where the proportion of susceptible persons may be greater than elsewhere.

Another point of interest concerning the recognition of Bornholm disease in Adelaide in 1957 is that the same year has been notable for its low poliomyelitis incidence, which may have followed the institution of Salk vaccination in the latter half of 1956. Dalldorf (1955) quotes numerous instances in which Bornholm disease or Coxsackie B viruses have been prevalent, whereas poliomyelitis has occurred infrequently or not at all. He notes and discusses exceptions to this finding, and it is of interest that Howes (personal communication) was successful in isolating Coxsackie viruses when a severe epidemic of poliomyelitis occurred in Adelaide.

The isolation of a Coxsackie B virus of type 2 from a patient with the clinical features of Bornholm disease, and the demonstration of a rising titre of neutralizing antibodies active against the virus in serum removed from the patient in the early and late stages of the disease, show for the first time the association of type B2 with myalgic disease. The association between type B2 and benign meningitis has been described before (Melnick *et alii*, 1950; Rhodes *et alii*, 1953; Hummeler *et alii*, 1954; Kirby and Evans, 1955); but the association between it and Bornholm disease, though expected, has not been described.

In Adelaide, Coxsackie B3 and B4 viruses have previously been isolated (Howes, 1951 and personal communication; Atkinson, Dineen and Robertson, 1951). Elsewhere in Australia type B3 has been isolated in Sydney (Stanley, Dorman and Ponsford, 1953) and type B4 in Queensland (Annual Report, 1954). Thus types B2, B3 and B4 have been detected in Australia, but not B1 or B5.

Our failure to isolate more than one strain of virus from 22 patients with Bornholm disease does not enable us to decide whether it is likely that one or more types of Coxsackie B virus were circulating in Adelaide at the time of our investigation. However, the isolation of two almost certainly identical strains from two patients with benign meningitis has indicated that Coxsackie B2 virus had a wide geographical and temporal distribution in 1957. Of the three patients whom we may reasonably associate with B2 infection, one fell ill in March and one in June. One of the patients lived on the northern perimeter of Adelaide and another on the southern perimeter.

Most authors, when attempting to isolate a virus from patients with Bornholm disease, were apparently successful in about half of the attempts (Warin *et alii*, 1953; Disney *et alii*, 1953; Lazarus *et alii*, 1952). Our proportion of successes is far less than these, but is something similar to that obtained by Cheever, Daniels and Hersey (1950), who isolated a virus from two of 19 stools examined from patients with presumed Coxsackie aseptic meningitis. It may be a characteristic of some Coxsackie infections that virus is scanty in the fæces.

The demonstration of neutralizing antibodies against the Kaiser strain of Coxsackie B2 virus in 13 of 24 patients shows that, at some time in the past, at least about half of them had been exposed to the virus. As the virus was widespread in Adelaide, it is reasonable to assume that it was responsible for many of the cases of Bornholm disease. For proof of this, however, the demonstration of rising antibody titres would be necessary. In only one of 11 of the Adelaide patients from whom serum was taken at appropriate times, was a rising antibody titre demonstrated. However, our experience is not unique, for Cheever, Daniels and Hersey (1950) were able to demonstrate neutralizing antibodies in only nine of their 18 patients, and of these only one showed a rising titre; Curnen, Shaw and Melnick (1949) demonstrated a rising titre in only one of 10 patients with antibodies. Others have been more successful; Girardi *et alii* (1957), using tissue culture, were able to detect rising titres in 23 of 25 patients, whereas the other workers mentioned all used suckling mice. Warin *et alii* (1953) were able to demonstrate rising titres in all but five of 13 patients with Bornholm disease. However, in another of their patients, from whom they isolated a virus, they were unable to demonstrate neutralizing antibody.

It may be that, with Coxsackie viruses which are of certain strains, or whose virulence is diminished, or which have become endemic, the antibody response to them is not marked, and that our methods were insufficiently sensitive to detect them. In addition to this, it may be that the invasion of virus and the antibody response to it often occur before the myalgic illness; this would account for the difficulty in isolating the virus, for the presence of antibodies in serum taken early in the disease and for the failure to detect a rising antibody titre. There is evidence to support the view that the myalgic phase is not necessarily the immunizing phase of the illness, in that it is well known that relapses are frequent in Bornholm disease, presumably in the presence of antibody.

If our suppositions are correct, it is possible to assume that one type of virus was the causative agent in the Adelaide cases of Bornholm disease, but that the diagnostic methods described were, in our hands, not helpful in individual cases. The alternative explanation, which we think is less likely, is that more than one type of virus was circulating in Adelaide and that we were only fortunate enough to isolate one.

## Summary.

This paper describes a laboratory and epidemiological study of 53 cases of Bornholm disease and two of benign meningitis. The outbreak of Bornholm disease appeared to be widespread in Adelaide, although there may have been a concentration of patients in a new housing estate. There was a preponderance of females, and most of the patients were aged from 20 to 54 years. The outbreak was unusually spread out over the whole year.

A Coxsackie group B type 2 virus was isolated from one patient, in whose serum a rising titre of antibodies against the virus was demonstrated. This established for the first time an association between Coxsackie B2 virus and Bornholm disease. Two viruses isolated from the patients with aseptic meningitis were almost certainly identified with the B2 strain obtained from the patient with Bornholm disease.

Among the sera of 24 patients with Bornholm disease, 13 had neutralizing activity against the isolated virus. Except in serum from the above-mentioned patient, no rising titres of antibodies could be demonstrated. In addition to the

successful isolations, unsuccessful attempts were made to isolate viruses from 21 patients and eight family contacts of patients.

The failure to isolate viruses and to demonstrate rising antibody titres is discussed, and it is thought that, in spite of this, it is possible that the whole outbreak may be attributed to Coxsackie B2 virus.

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## HYDROCORTISONE AND PREDNISOLONE IN RHEUMATOID ARTHRITIS.

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MANY years ago Hench postulated a "substance X", which, circulating in the blood during pregnancy, jaundice and starvation, had the power to reverse some of the changes which occur in rheumatic disease. Since then we have had his dramatic report of the first case in which a patient suffering from rheumatoid arthritis was treated with cortisone (Hench *et alii*, 1949). Later hydrocortisone became available, and somewhat better results were reported.

Owing to mass production and ready availability, these drugs were used promiscuously, and as usual an avalanche of reports, both good and bad, led finally through longer-term observations to the report of the Joint Committee of the Medical Research Council and Nuffield Foundation. This committee reported that "for practical purposes . . . there appears to have been surprisingly little to choose between cortisone and aspirin . . . in the early stages of rheumatoid arthritis". (Report of Joint Committee, 1954 and 1955). As a result the limitations of these steroids have been recognized and the following difficulties inherent in their use are well known: (i) the benefits are temporary and there is a tendency for the disease to break through the artificial steroid barrier; (ii) the dose is pharmacological and not physiological, leading to suppression of the suprarenal cortex and of the anterior pituitary lobe with undesirable side effects; (iii) overdosage may cause hypercorticalism; (iv) coexisting pathological conditions may be aggravated.

For these reasons, research is proceeding in an effort to produce a synthetic product which will result in both maximal suppression of the disease and a minimum of undesirable effects. While it is realized that the adrenal steroids are only suppressive, it should not be forgotten that if they are able to be maintained as therapeutic agents the process which has led to the rheumatoid disease may in some cases be reversed in time and normal physiology restored at the target point, which appears to be in the collagen material of connective tissue.

Modification of the steroid molecule has recently resulted in the preparation of prednisone and prednisolone (derivatives of cortisone and hydrocortisone, respectively Δ dehydro-cortisone and Δ dehydro-hydrocortisone). Generally, it is considered that these two substances are identical in their anti-rheumatic effect, and that they have a potency three to five times that of cortisone and hydrocortisone acetate taken by mouth (Hart *et alii*, 1955). However, Forsham *et alii* (1955), using the urinary 17-hydroxycorticosteroids as an index of activity, showed that prednisolone was about 20% more potent than prednisone, which fact is in keeping with the recognized relationship of the parent steroids. Hollander (1955) compared prednisone and prednisolone in 31 cases of rheumatoid arthritis and other conditions known to respond favourably to cortisone or hydrocortisone, with results as follows: greater relief from prednisolone, 17 cases; greater relief from prednisone, three cases; equal relief, 11 cases. Seven patients who were "escaping" on prednisone recovered their improvement when they were changed to prednisolone. Further, with continued therapy, 11 of the 31 patients were maintained on a daily dose of prednisolone smaller by five milligrammes than the dose previously required of prednisone.

We now have drugs with enhanced therapeutic effect. Early reports of these have shown that the undesirable qualities are lessened; longer-term studies show that most of the above-mentioned limitations still apply, although to a lesser extent than with the earlier steroids (Hart *et alii*, 1955; Margolis *et alii*, 1955; Bollet *et alii*, 1955; Spies *et alii*, 1955; Dordick *et alii*, 1955; Bunim *et alii*, 1955; Kelly, 1956; Boland, 1956).

Sodium retention and œdema are major problems when cortisone and hydrocortisone are used, often preventing the effective presentation of these drugs. When the modified

TABLE I.

*Results of Blind Trial to Test Hydrocortisone and Prednisolone in Rheumatoid Arthritis.*

| Case Number. | Sex. | Age in years | Duration of Illness. (Years.) | Condition. | Stage. | Class. | Hydrocortisone. | | | | | | Prednisolone. | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Dosage (Milligrammes per Day). | Duration (Weeks). | Class. | Grade. | Erythrocyte Sedimentation Rate.[1] Before. | Erythrocyte Sedimentation Rate.[1] After. | Remarks. | Immediate Improvement. | Duration (Weeks). | Class. | Grade. | Erythrocyte Sedimentation Rate.[1] | Maintenance Dosage (Milligrammes). | Remarks, Withdrawal and Resubstitution. |
| 1 | F. | 36 | 17 years. | Subacute, active joint inflammation, destruction, nodules, anæmia, œdema. | 4 | 3 | 40 | 10 | 2 | 2 | 54·0 | 20·0 | Œdema, round rosy face, nervousness; adequate, smooth response. | + | 17 | 2 | 1 | 5 | 7·5 | Increased response on prednisolone—loss of œdema. Response continued for two weeks on substitution of hydrocortisone, then œdema occurred, nervousness returned and general condition declined to 35th week, when prednisolone again relieved her. |
| 2 | M. | 64 | 4 years. | Acute disease, chronic sinusitis and bronchitis; nodules, anæmia, L.E. phenomenon in blood. | 4 | 2 | 40 | 64 | 2 | 2 | 18·5 | 15·0 | Nervousness marked, fair response; tendency to escape, œdema, improvement in blood picture, loss of L.E. phenomenon. | + | 20 | 2 | 2 | 13 | 10·0 | Sudden withdrawal with pneumonitis finally diagnosed as pulmonary tuberculosis. No marked symptoms followed to 39th week. Some root pain in arms at present due to long period of rest in bed. |
| 3 | F. | 65 | 18 months. | Acute; pale, puffy, sweaty hands hands and feet, great fatigue, anæmia and debility. | 2 | 3 | 40 | 16 | 2 | 2 | 22·0 | 16·0 | Reduction in all symptoms; tendency to escape shown. | + | 10 | 1 | 2 | 14 | 10·0 | Exacerbation in two days on reduction to 5·0 milligrammes daily. Gradual improvement again on 10 milligrammes, continuing; dyspepsia. |
| 4 | M. | 72 | 9 years. | Low-grade general activity. | 4 | 3 | 60 | 12 | 2 | 3 | 14·0 | 12·0 | Moon-face, massive œdema, indigestion. | − | 2 | — | — | — | — | Prednisolone less effective despite lack of œdema. Hydrocortisone later, no effect. Indigestion severe; melæna, clammy hands throughout. Ecchymotic lesions. |
| 5 | M. | 47 | 2½ years. | Acute onset following cement poisoning; generalized, great pain and stiffness. | 4 | 4 | 60 | 36 | 4 | 3 | 18·0 | 13·0 | Gradual improvement; never quite complete control. | + | 12 | 3 | 2 | 20 | 12·5 | Still under treatment, destruction of hip joints rapid. Inadequate maintenance—sweatiness, vascular abnormalities, purpuric spots and ecchymotic lesions, dyspepsia. |
| 6 | F. | 4 | 18 months. | Low-grade joint disease, marked constitutional symptoms. | 2 | 2 | 20 | 15 | 2 | 3 | 17·0 | 9·0 | Moon-face, rapid pulse, clammy hands, adequate response. | + | 18 | 2 | 2 | 19 | 5·0 | Still under treatment, well; full range of movement in most joints. Pulse rate still high. Still clammy. Slight moon-face. |
| 7 | F. | 64 | 6 months. | Acute joint and general symptoms six weeks after "influenza" | 2 | 3 | 60 | 6 | 2 | 2 | 51·0 | 24·0 | Œdema of legs. Moderate relief, difficult to establish on drug, indigestion. | + | 18 | 2 | 2 | 28 | — | Tendency to escape. Dyspepsia. Auricular fibrillation necessitated withdrawal. |
| 8 | F. | 19 | 4 years. | Acute general disease after upper respiratory tract infection relieved by bed rest and salicylates. Moderate joint and marked constitutional symptoms. | 3 | 2 | 40 | 14 | 2 | 1 | 16·0 | 11·0 | Marked improvement; acne and moon-face. | + | 15 | 1 | 1 | 5 | 5·0 | After withdrawal, maintenance on phenylbutazone to 41st week free of active disease. |
| 9 | F. | 50 | 3½ years. | Subacute disease, severe in wrists and fingers, making her almost useless, psoriasis. | 2 | 3 | 30 | 16 | 2 | 2 | 10·0 | 15·0 | Able to do housework again. | + | 6 | 1 | 1 | 4 | 5·0 | Maintained satisfactorily on 5·0 milligrammes to date. Dyspepsia mild and some signs of hypercorticalism appearing. Vague muscle pains and fatigue, occasional joint swelling and pain. |
| 10 | F. | 61 | 9 years. | Generalized disease following bronchitis—elbows, hands and feet mainly; nodules, cyanotic, extremities puffy and cold. | 3 | 3 | 40 | 40 | 2 | 2 | 16·0 | 13·0 | Good control, tended to escape. Moon-face, œdema. | + | 22 | 1 | 1 | 4 | 5·0 | Accidental withdrawal; exacerbation, relief on return. Dose reduced to 5·0 milligrammes daily with satisfactory maintenance. Nodules gone. Blood picture improved. Usual recurrent sinusitis and bronchitis not appearing. |
| 11 | F. | 48 | 3 years. | Widespread early damage and ankylosis. Nodules. | 4 | 4 | 40 | 10 | 4 | 3 | 21·0 | 11·0 | Moon-face, slight depression relieved. | + | 14 | 2 | 2 | 9 | — | Remission. Ecchymotic lesions, less moon-face, no œdema. |
| 12 | M. | 14 | 5 years. | Rheumatic fever followed by rheumatic pains, very tender peripheral interphalangeal joints. | — | — | 30 | 3 | — | — | 5·0 | 7·0 | No improvement; continued to have intermittent fever. | + | 5 | — | — | 5 | 15·0 | Little alteration; intermittent feverish attacks, maintained puffy, clammy hands, muscular pains of hypercorticalism type; probably psychogenic. |
| 13 | M. | 44 | 3 years. | Acute onset after pneumonia; rapid deformity and ankylosis; no L.E. phenomenon. | 4 | 2 | 40 | 10 d. | — | — | — | — | Generalized œdema; pleural effusion; suspended. | − | — | — | — | — | — | Later trial of prednisolone; intense excitability, marked dyspepsia; little relief in the few days of treatment. |

TABLE I.—*Continued.*

*Results of Blind Trial to Test Hydrocortisone and Prednisolone in Rheumatoid Arthritis.*—Continued.

| Case Number. | Sex. | Age in years | Duration of Illness. (Years.) | Condition. | Stage. | Class. | Hydrocortisone. | | | | | | Prednisolone. | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Dosage (Milligrammes per Day). | Duration (Weeks). | Class. | Grade. | Erythrocyte Sedimentation Rate.[1] Before. | Erythrocyte Sedimentation Rate.[1] After. | Remarks. | Immediate Improvement. | Duration (Weeks). | Class. | Grade. | Erythrocyte Sedimentation Rate.[1] | Maintenance Dosage (Milligrammes). | Remarks, Withdrawal and Resubstitution. |
| 14 | F. | 68 | 12 years. | Old generalized; osteoarthritis; rheumatoid disease for six months. | 4 | 2 | 60 | 3 | 4 | 2 | 21·0 | — | Inadequate control. œdema, tachycardia; difficult to establish on drug. | + | 2½ | — | — | — | 20·0 | Suspended owing to onset of pleurisy; exacerbation. Responding to second course poorly, but nursing is easier, sleeping with less sedation. Ecchymotic lesions and severe dyspepsia. Tachycardia. |
| 15 | M. | 38 | 2 years. | Following non-specific urethritis, mainly hands and feet; marked general symptoms. | 2 | 2 | 40 | 7 | 2 | 2 | 19·0 | 18·0 | No adverse symptoms. | + | 14 | 2 | 2 | 14 | 10·0 | Greater relief from prednisolone; less benefit when hydrocortisone tried again. |
| 16 | F. | 9 | 6 years. | Active disease in ankle; restricted shoulders, elbows and fingers. | 2 | 2 | 20 | 12 | 2 | 2 | 29·0 | 17·0 | No adverse symptoms. Moon-face. | + | 14 | 2 | 2 | 12 | 5·0 | Progressive improvement. Clammy hands, tachycardia. |
| 17 | F. | 36 | 9 months. | Acute local and general. | 3 | 2 | 60 | 9 | 2 | 2 | 54·0 | 22·0 | Moon-face, œdema. Moderate control. | + | 9 | 2 | 2 | 27 | 15·0 | Still under treatment. Flushes and sweating. Tending to escape. |
| 18 | F. | 35 | 2 months. | Penicillin reaction after pharyngitis; L.E. phenomenon. | 3 | 1 | 60 | 1 | — | — | — | — | Marked œdema of legs. | + | 16 | 1 | 1 | 8 | 15·0 | Joint stiffness still present. L.E. phenomenon not demonstrated after five weeks. Mild dyspepsia; continuing. |
| 19 | M. | 64 | 4 years. | Disseminated *lupus erythematosus* relieved by chloroquin; six months' joint pains and swelling. | 1 | 1 | 40 | 23 | 1 | 1 | 32·0 | 9·0 | Decrease in generalized erythema. | + | 11 | 1 | 1 | 14 | 10·0 | Well maintained to date. No side effects. |
| 20 | F. | 55 | 5 years. | Near albino. Great pain, swelling and pallor of hands and feet. | 2 | 2 | 40 | 15 | 2 | 2 | 17·0 | 11·0 | Mild œdema, improved circulation. Adequate response. | + | 14 | 2 | 2 | 11 | 10·0 | Three attacks of thrombophlebitis in right arm. Two abscesses in feet from ingrowing toe-nails. Dyspepsia; continuing. |
| 21 | F. | 31 | 6 months. | Sinusitis treated with penicillin and "Achromycin". Disseminated *lupus erythematosus* followed. | 1 | 1 | 40 | 5 | 1 | 1 | 25·0 | 10·0 | Good response. | + | 9 | 1 | 1 | 14 | 10·0 | On withdrawal still weak, fatigued, pale and asthenic, sweating. Fleeting joint and muscle pains. |
| 22 | M. | 55 | 2½ years. | Severe, great synovial swelling. Severe general symptoms. | 3 | 3 | 60 | 15 | 2 | 3 | 21·0 | 20·0 | Average control. | + | 23 | 2 | 2 | 16 | 15·0 | Destruction of elbows has advanced rapidly, returned to work. Ecchymotic lesions gradually improving. Accidental withdrawal; exacerbation on one occasion. |
| 23 | F. | 66 | 19 years. | Ulcerative colitis, chronic urogenital disease, generalized joint symptoms. | 3 | 2 | 15 | 12 | 2 | 3 | 19·0 | 21·0 | Relief of joint pains slight. | + | 14 | 2 | 2 | 25 | 7·5 | Relief of joint pains, little difference to general and local disease. Could tolerate only 7·5 milligrammes of prednisolone after a time because of diarrhœa and colic. Ecchymotic lesions and dyspepsia. |
| 24 | F. | 5 | 6 months. | Gradual increase in disease despite bed rest and salicylates. | 2 | 3 | 30 | 15 | 2 | 2 | 14·0 | 9·0 | Moon-face, relief, slow increase in range of movement. Indigestion. | — | 19 | 2 | 1 | 5 | 5·0 | Improvement slow, but more noticeable on prednisolone. Clammy hands and tachycardia. |
| 25 | F. | 8 | 4 years. | Rheumatic fever at four years, gradual development of rheumatoid arthritis. | 2 | 2 | 30 | 9 | 2 | 2 | 9·0 | 11·0 | Adequate relief. | + | 8 | 2 | 1 | 4 | 5·0 | Apparent remission to 14 weeks after withdrawal. |
| 26 | F. | 58 | 10 years. | Reiter's disease. | 4 | 4 | 60 | 27 | 3 | 3 | 22·0 | 18·0 | Moon-face. Fat pads, œdema, indigestion. | — | 31 | 3 | 3 | 27 | 15·0 | Marked relief of œdema, moon-face and fat pads. Maintenance allows easier nursing in rest home. Ecchymotic lesions dyspepsia mild, sweating of hands and feet. |
| 27 | M. | 28 | 3 months. | Bronchitis treated with "Achromycin" produced *status asthmaticus*. ACTH to relieve the condition; rheumatoid arthritis on withdrawal. | 2 | 3 | 60 | 14 | 1 | 1 | 7·0 | 5·0 | Well controlled. | + | 9 | 1 | 1 | 9 | 10·0 | On withdrawal, recurrent joint and muscle pains. Rheumatoid swelling and stiffness recur when under stress. Remarkable increase of emphysema noted. |
| 28 | M. | 43 | 1 year. | Chronic low-grade disease. | 1 | 1 | 40 | 10 | 1 | 1 | 9·0 | 11·0 | Well controlled. | + | 4 | 1 | 1 | 7 | 10·0 | Slight hypercorticalism developed; withdrawal, slow return to previous state. Vascular and ecchymotic lesions. |

[1] Westergren method: millilitres in one hour.

steroids are used, not only is there a lack of retention of salt and water by the patient, even when excess is given and even on high dosage of steroids, but also a diuresis frequently occurs. Blood pressure does not rise, which is another obviously valuable quality. Improvement in the blood picture has been noted. There is no significant loss of nitrogen (Boland, 1956; Bunim *et alii*, 1955). This is a feature of cortisone and hydrocortisone therapy and is a factor in osteoporosis with destruction and collapse of bone —a complication to be considered.

Suppression of the 17-ketosteroid excretion is noted. Therapeutic doses do not produce physiological side effects to the same extent as the other steroids. Hirsuties, acne, facial rounding, fat pads and irritability are seen only in minor degree (Bunim *et alii*, 1955); but reduction of carbohydrate tolerance, although not seen with smaller dosage, has been reported. Nabarro *et alii* (1955) have recorded the onset of steroid diabetes in two patients who had had high dosage of prednisone.

Thus it appears that the modified steroids exert a somewhat selective suppression of the suprarenal cortex and the anterior pituitary lobe.

Despite earlier reports on short-term studies which failed to show major effects on the intestine, brain and other systems, gastric irritation and ulceration (which may be symptomless), depressive psychoses and activation of infective diseases may appear (Boland, 1956; Bollet *et alii*, 1955; Cohen *et alii*, 1955; Margolis *et alii*, 1955). All these authors point to the improvements to be expected from the use of new steroids, and to the possibilities of further enhanced activity with new modification of the steroid molecule.

So, prednisone and prednisolone, as they are of greater potency, can be used in smaller dosage to obtain a greater antirheumatic effect and can, to a certain extent, lessen undesirable side effects and alteration to the general metabolism.

The report of a blind trial to test the relative efficacy of hydrocortisone and prednisolone as antirheumatic agents and to assess the importance of adverse effects and physiological alteration in each case, is presented below. Tablets of hydrocortisone (20 milligrammes) and prednisolone (five milligrammes), identical in appearance and unidentifiable by size or shape, were prepared by the Upjohn Company, Kalamazoo, Michigan, U.S.A., for this purpose.

## Procedure.

Twenty-eight unselected patients suffering from rheumatoid arthritis in all stages of activity and progress, each with active disease involving several peripheral joints, were taken for study. Four other patients, who were to have been included and who could not be established on hydrocortisone because of early onset of side effects, were dropped from the study.

Preliminary examination of the patients obtained a base line for subsequent results, and the patients were then established on a sufficient dose of hydrocortisone to bring about a reasonable and measurable remission of symptoms without any attempt to produce maximal improvement. The dose, which varied from 20 to 60 milligrammes daily, was considered satisfactory when a positive, continuous, subjective and objective improvement was noted and maintained. Considerable difficulty occurred at this stage in some cases, necessitating frequent adjustments and withdrawals before the patients could be satisfactorily controlled.

After varying intervals, comparative tests of function and improvement were carried out, laboratory investigations were performed, and without the knowledge of the patients or of their nursing or physiotherapy attendants a change was made, tablet for tablet, to prednisolone. After a time, when possible, and while the same degree of improvement was being maintained, a gradual reduction of dosage was undertaken.

After a further interval the prednisolone was tapered off and withdrawn abruptly, hydrocortisone was substituted or prednisolone was continued. Further comparative observations were made.

During the experiment no other antirheumatic remedies were used, but many patients are known to have taken various types of salicylate preparations at times. Some patients whose disease was active were nursed in bed in the initial stages; all were given any necessary physiotherapy and splinting and were managed as far as possible on an ambulatory regime.

In recording the findings, note was taken of the patient's over-all improvement assessed by general constitutional well-being, subjective and objective observations and measurements, functional capacity and laboratory investigation. Detailed examinations of involved joints were made by physiotherapists who, while knowing that the patients were taking steroid therapy, were ignorant of the drug and any changes in the specific steroid. The patients were classified according to the scheme of Steinbrocker *et alii* (1949), which takes note of the stage of development of the disease, the class of incapacity and the grade of improvement. The stage and class are shown as 1 to 4 in increasing severity, and the grade as 1 to 4, grade 1 being the greatest and grade 4 the least improvement. (See Table I.)

In reading the above results, it must be remembered that to some extent the patient's response to prednisolone is affected by previous hydrocortisone therapy and by the duration of therapy, but those patients who were put back on hydrocortisone experienced some decline in improvement, even within 48 hours, indicating that they were in fact, better while taking an equivalent dose of prednisolone. The pattern of return of symptoms on withdrawal of prednisolone varied. In general there was a vague decline in well-being after the first day. This persisted and increased to a general exacerbation in most cases. In some it was relieved by the reinstitution of treatment, when given; but in patients who showed apparent remission the exacerbation gradually increased for about one week, and then a slow improvement occurred over the subsequent two to three weeks and was maintained.

## Assessment.

### *General.*

As was recorded above, improvement in general condition occurred with hydrocortisone. Almost all patients commented on an added improvement after transfer to prednisolone, many noted without questioning that they had some polyuria and loss of œdema, and many commented on improvement in joint status and movement and relief of pain even within the first week of the change. These subjective changes were borne out by definite objective improvements.

### *Joints.*

One of the most severely affected patients (Case 2) showed considerable improvement in range of movement, despite substantial permanent joint damage. The measurements of the large joints on the right side of his body were as shown in Table II. This man had achieved maximum improvement on hydrocortisone and was showing signs of escaping (64 weeks of treatment) when transferred to prednisolone. Despite this, he felt improvement with the change and had a further improvement in joint range.

Many of the less severely affected persons had a much greater improvement than this patient; some with minimal joint destruction appeared normal in every respect.

The change of class and the grade of improvement are shown in the preceding records of cases (Table I).

### *Laboratory Findings.*

The blood picture in these cases did not show such significant changes as have been recorded by others (Bunim *et alii*, 1955). There was a definite hæmoglobin increase in many patients taking prednisolone which was not shown while they were taking hydrocortisone.

The erythrocyte sedimentation rate was generally reduced on hydrocortisone therapy, and in many cases a further reduction was secured when prednisolone was substituted, but again the changes were not so dramatic as have been reported.

Chemical examination of serum proteins showed a return towards normal values, well exemplified by the findings in

Case 8 (Table III). Electrophoretic analysis generally showed a slight fall in the gamma globulin; alpha 2 and beta globulin tended to remain elevated, but at a slightly lower level. Changes were more definite after prednisolone than after hydrocortisone.

*Estimation of 17-Ketosteroids in the Urine.*

In general, a moderate decline in the excretion of 17-ketosteroids, as in Case 4, was shown. These figures do not bear out the sharp fall reported by Bunim *et alii* (1955), who were using a much larger dosage.

*Sodium and Water Retention.*

The Robinson-Power-Kepler test was used in Cases 2, 5 and 6. The patient in Case 5 gave a constant of greater than 25 while receiving hydrocortisone; this figure fell to 11 with prednisolone. In the other two cases the figures were reported as being in normal limits on both occasions. Thus water and salt balance was not disturbed by prednisolone in moderate therapeutic dosage.

TABLE II.

*Range of Movement of Large Joints on Right Side.*

| Joint. | Before Treatment. | After Hydrocortisone. | After Prednisolone. |
|---|---|---|---|
| Shoulder: | | | |
| External rotation .. | 15° | 25° | 30° |
| Internal rotation .. | 10° | 10° | 40° |
| Abduction .. .. | 60° | 75° | 105° |
| Flexion .. .. | 75° | 120° | 180° |
| Extension .. .. | 5° | 10° | 20° |
| Elbow range .. .. | 95°–60° | 120°–25° | 130°–25° |
| Hip range (flexion) .. | 0°–90° | 0°–120° | 0°–140° |
| Knee range .. .. | 165°–120° | 180°–60° | 180°–95° |
| Ankle range .. .. | 90°–100° | 90°–125° | 90°–130° |

*Insulin Sensitivity Test.*

Case 10 illustrated the sensitivity to insulin in the three phases of examination. With hydrocortisone there was a late reaction and slow recovery by the patient, while with prednisolone the reaction and recovery were parallel to the findings before treatment.

The findings of Nabarro, who was using much larger dosage, were not repeated in this series. Simple examination of the urine of all patients failed to reveal sugar at any time. It must be noted that testing of the urine for sugar may not be a true index.

**Undesirable Side Effects in Series of 28 Patients.**

The average figure for peptic ulcer from the literature is about 7%. It is thought that figures would be higher if more barium-meal X-ray examinations were made. Barium meal X-ray examinations were not carried out except on the one patient with hæmorrhage, in whom no ulcer was revealed. Adequate treatment with "Amphogel" lessened the severity of dyspepsia in most cases. These figures tend to support the contention that when there is a history of gastro-intestinal disease hydrocortisone is a safer drug than prednisolone. In reverse, prednisolone is the drug of choice for the older group of patients or for those in whom there is any doubt about the cardio-vascular status, so that a calculated risk must be taken.

Coexisting pathological conditions were activated in eight cases. Chest lesions interrupted treatment in three cases; one patient developed a troublesome cough and findings of bronchitis, a second developed pleurisy, a third was proved to have pulmonary tuberculosis, and a fourth showed an unusual increase in emphysema. In each case X-ray examinations prior to treatment showed no active lesions, but all patients had had a history of respiratory disease. One patient, aged 64 years, suffered auricular fibrillation while taking prednisolone. She was given hydrocortisone for six weeks only, because of marked œdema of the legs. The patient in case 23, who had a long history of colitis, vaginal discharge and renal tract disease, did not improve with hydrocortisone, but she improved for a short time with prednisolone and finally could take only 7·5 milligrammes daily because of aggravation of the colitis. She had slight benefit in regard to her joints.

Two patients showed very rapid joint degeneration. In Case 5, although the condition was moderately controlled generally, rapid destruction and ankylosis of the hip joints occurred. Another patient (Case 22) returned to work as a night watchman, despite very severe pain in the elbows; he was unrelieved by splinting and it was assumed that the pain was due to rapid bone destruction.

TABLE III.

| Time of Estimation. | Biuret Reaction: Serum Protein Content (Grammes *per Centum*). | Thymol Turbidity. (Units.) | Zinc Sulphate Turbidity. (Units.) |
|---|---|---|---|
| Before trial .. .. | Total 7·8 (albumin 4·5, globulin 3·3) | 4·9 | 6·8 |
| After hydrocortisone | Total 6·5 (albumin 3·9, globulin 2·6) | 2·3 | 2·8 |
| After prednisolone | Total 6·2 (albumin 4·2, globulin 2·0) | 2·4 | 1·8 |

In a review of the limitations of steroid therapy, it is found that all the previous difficulties still exist, although some have been lessened and some have been increased.

Four patients are in true remission, but this means little, since such a proportion can be obtained in any group of patients once they come under supervision. The tendency to break through the artificial steroid barrier, although seen frequently with hydrocortisone, was less noticeable with prednisolone in this short-term study.

TABLE IV.

*Undesirable Side Effects in Series of 28 Patients.*

| Side Effect. | During Hydrocortisone Therapy. | During Prednisolone Therapy. |
|---|---|---|
| Increase in weight .. .. .. .. | 17 | 1 |
| Œdema of legs .. .. .. .. | 11 | 0 |
| Rounding of face .. .. .. .. | 10 | 2 |
| Hirsuties .. .. .. .. .. | 5 | 2 |
| Excessive appetite .. .. .. .. | 1 | 1 |
| Mild dyspepsia .. .. .. .. | 7 | 6 |
| Marked dyspepsia .. .. .. .. | 4 | 7 |
| Hæmorrhage .. .. .. .. | 0 | 1 |
| Ecchymotic lesions .. .. .. .. | 0 | 7 |
| Sweating .. .. .. .. .. | 2 | 7 |
| Restlessness .. .. .. .. .. | 6 | 1 |
| Mental disturbance .. .. .. .. | 1 | 0 |
| Weakness .. .. .. .. .. | 5 | 2 |
| Skin pigmentation .. .. .. .. | 1 | 4 |
| Thrombophlebitis .. .. .. .. | 0 | 4 |
| Abscess formation .. .. .. .. | 0 | 2 |

The suppression of the suprarenal cortex has been demonstrated by depression of 17-ketosteroid excretion. The results indicate also that with prednisolone it is a selective suppression and lend hope to future development of a more perfect steroid product for suppression of the effects of collagen disease.

The selective suppression is supported by the remarks of Bunim *et alii* (1955), who found that relatively small doses of prednisolone were required to suppress the withdrawal symptoms that followed the sudden withdrawal of cortisone; however, when the new steroids were gradually withdrawn from a patient who had previously received prolonged cortisone administration, severe constitutional symptoms might follow. Further, Brown has a case in which a Δ-steroid induced Addisonian crisis was apparent in a patient undergoing treatment.

The symptoms of cortical suppression under this programme were not so marked with prednisolone as with hydrocortisone, nor did the laboratory tests indicate the same over-all degree of depression; but among the children studied vasomotor changes and tachycardia were a constant problem with both hydrocortisone and prednisolone. Slowing down of the rate of growth in children was noted during treatment; a quite rapid increase was seen on suspension of treatment. Intermittent treatment would therefore seem advisable in young children.

Major hypercorticalism was not demonstrated in this series, since in most cases the therapy was of short duration. Also, coexistent pathological conditions were not aggravated to any extent. It may be noted that two patients with long histories of respiratory symptoms and episodes were free of trouble through the trial, although one did present pulmonary tuberculosis after 84 weeks of steroid therapy. Four patients could not be established on steroid therapy at the commencement of the trial because of side effects, and in four cases under review these side effects interfered with treatment.

### Conclusion.

Prednisolone reverses and suppresses many of the changes brought about by rheumatoid arthritis more than four times as effectively as hydrocortisone. The side effects and changes in metabolism which make treatment with hydrocortisone difficult to maintain, although mainly present, are less troublesome in treatment with prednisolone in comparative dosage.

### Acknowledgement.

I wish to thank the Upjohn Company, Kalamazoo, Michigan, U.S.A., for the generous supply of tablets used in this trial.

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### Addendum.

Twelve months after the completion of this trial the situation may be reported as follows:

Remission maintained: Cases 2, 8, 25.

Exacerbation: Cases 6, 11.

New remissions: Cases 10, 17, 18.

Maintenance of good functional condition: Cases 19, 22.

Maintenance of fair functional condition: Cases 5, 9, 23, 24, 26.

Increasing activity: Cases 1, 3, 20, 21.

Hypercorticalism: Cases, 1, 3, 9, 20.

Lost to trial: Cases 4, 7, 14.

Rehabilitated in varying degree: Cases 5, 12, 13, 15, 27, 28.

More than ever I am impressed with the need for the greatest care of damaged joints, especially weight-bearing joints, while the patient is taking steroid medication. The increasing destruction of joints, due to many factors but fundamentally related to relaxation of the protective pain mechanism, has been a cause of considerable concern.

## SERUM TRANSAMINASE: THE DIAGNOSTIC VALUE OF THE ESTIMATION IN CARDIAC INFARCTION AND LIVER DAMAGE.[1]

By NOEL M. GUTTERIDGE AND CORAL J. MCKEAN, B.Sc. (Queensland).

(From the Medical Research Foundation, Brisbane, Queensland.)

THIS report provides a survey of the literature, a technical comparison of the methods of assay available with the selection of a dependable and workable method, and the results of 200 separate assays.

Glutamic-oxalacetic transaminase is abundant in many animal tissues, and was first shown by Cohen (1941) to be particularly abundant in cardiac and skeletal muscle. The enzyme catalyses the reversible transfer of amino-nitrogen of aspartic acid to α-ketoglutaric acid, with the resultant synthesis of a second amino acid—glutamic acid—and oxalacetic acid (Figure I).

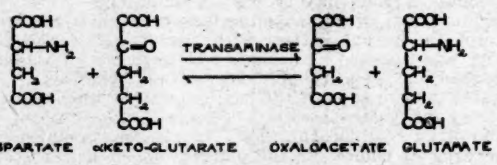


FIGURE I.
The transamination reaction.

The enzyme has been found in all normal serum so far tested. The highest concentrations are found in heart muscle, skeletal muscle, brain, liver and kidney in that decreasing order. If a significant degree of cell damage or destruction occurs in any of these tissues rich in glutamic oxalacetic transaminase, the enzyme is liberated from the damaged cells into the blood, with a resultant rise in serum glutamic oxalacetic transaminase (S.G.O.-T.)

[1] Read at the annual meeting of the College of Pathologists of Australia, University of Sydney, August 22 to 24, 1957.

level. The numerical value obtained in the serum is related to the product of the amount of tissue destroyed, multiplied by the enzyme content of the involved tissue.

Over the past three years, J. S. La Due, F. Wroblewski and co-workers in New York have studied the serum level of this enzyme in healthy persons, in patients with various cardiac conditions including myocardial infarction, and in a wide variety of other disease states, notably those involving acute damage of liver tissue.

La Due, Wroblewski and Karmen (1954) first described a two to 20 fold increase in the S.G.O.-T. level following myocardial infarction. From their studies, they concluded that S.G.O.-T. activity rose within 12 to 24 hours after acute human myocardial infarction and returned to normal range within three to six days. This has been fully confirmed by all other investigators who have studied this phenomenon. In view of the elevation following damage of heart muscle cells, Wroblewski and La Due (1955*b*) later undertook a study of S.G.O.-T. changes in diseases involving liver cell injury. Enormous elevations of S.G.O.-T. level had been recorded in toxic and infectious hepatitis, with a characteristic rise to a peak level and then a fall back to normal range, as the patient passes into the recovery phase of the disease.

The enzyme is unusually stable. Refrigerated serm (0 to 5° C.) has no appreciable loss in activity after 14 days, and freezing preserves activity for six months. Observations on the stability of the enzyme by Sobel *et alii* (1956) showed that in serum kept at room temperature (25° C.) for 19 days there was no significant decrease in S.G.O.-T. level, although there was conspicuous bacterial growth.

### Methods of Assay.

Figure II shows the four methods available for determination of S.G.O.-T. level. Both the chromatographic and colorimetric methods depend on the measurement of the quantity of end product produced in a definite time, when the enzyme and substrate are incubated at the optimum pH and temperature. In the spectrophotometric method, transaminase activity is measured as the reaction proceeds. Let us consider the general features of these four methods available, and their suitability in the clinical laboratory.

#### Chromatographic Method.

The amount of glutamate produced after a given incubation period under standard conditions (18 hours at 37° C.) is measured by quantitative paper chromatography, the steps in which may be set out as follows:

1. Enzymatic conversion.

$$\text{Aspartate} + \alpha\text{-ketoglutarate} \xrightarrow{\text{S.G.O.-T.}} \text{glutamate} + \text{oxaloacetate}$$

Incubate serum and substrate for 18 hours at 37° C

2. Precipitation of proteins with absolute alcohol. This stops the transamination reaction. Centrifuge.
3. Concentration of the glutamate in the supernatant. Evaporation of supernatant→residue, which is dissolved in phosphate buffer.
4. Estimation of glutamate by quantitative paper chromatography. Descending method for 18 hours in a phenol/$H_2O$ system. Elution of areas of glutamate by the method of Troll and Cannan (1953). Optical density determined at 570 mμ.

The method was initially used by La Due, Wroblewski and Karmen for research on S.G.O.-T. level after myocardial infarction. Values of 0·41 to 1·36 micromole per hour per millilitre were obtained in normal serum (mean, 0·622; standard deviation, ± 0·191). It is a lengthy and tedious (40 hours) procedure, and despite a fair degree of accuracy, is little used now, as other more accurate and less time-consuming techniques have replaced it.

#### Spectrophotometric Method.

The spectrophotometric method of Karmen (1955) couples the transamination reaction *in vivo* with the oxidation of reduced diphosphopyridine nucleotide (DPNH), in the presence of malic dehydrogenase (Figure III). Reduced DPN has a light absorption peak at 340 millimicrons, and the decrease in optical density at 340 millimicrons, as it is oxidized, is used to measure the transaminase activity of the serum. The reaction is followed at room temperature in a Beckman model DU spectrophotometer.

Aspartate, malic dehydrogenase, DPNH and serum are added to the cell and left in the spectrophotometer for about 10 minutes before α-ketoglutarate is added to complete the transamination system, because optical density falls during this period owing to oxidation of a small but finite quantity of DPNH. After this, optical density remains constant until α-ketoglutarate is added. Thereafter there is a steady decrease in optical density, which is taken as a measure of transaminase activity of the serum. One unit of S.G.O.-T. equals a decrease in optical density of 0·001 per minute per millilitre of serum at room temperature at 340 millimicrons. Since Karmen published his original method, other modifications have been published.

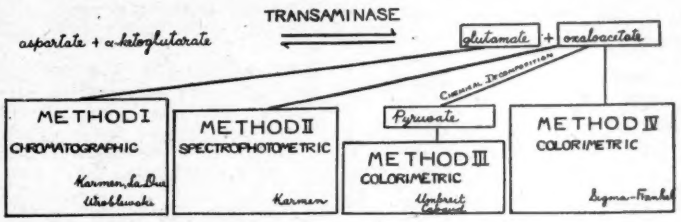


FIGURE II.
Various methods of S.G.O.-T. assay.

Sobel *et alii* (1956) concluded from their study that serum blanks were unnecessary, and preferred the use of stable reference blanks such as a thiamine glass block and 0·005N potassium dichromate solution. The advantages of using stable reference blanks were stated to be as follows: (*a*) the saving of costly reagents; (*b*) the fact that three unknown samples of serum could be read instead of two in the four cell carrier.

A popular modification of the original Karmen method is that of Hergt and Langin (1957). These workers employ only serum and buffer in their blank—a modification which in no way affects the measure of enzyme activity, and results in increased simplicity of technique, conservation of labour and greater economy of materials.

The spectrophotometric method is speedy and accurate and is the one of choice for research. It suffers the disadvantages of requiring expensive apparatus and unstable reagents, which are costly, difficult to obtain and require careful handling. However, in a laboratory with the necessary facilities, this need not be considered. The approximate time for the estimation is 30 minutes.

#### Colorimetric Method.

In the colorimetric method of Umbreit *et alii* (1957) and Cabaud *et alii* (1956), serum and substrate are incubated for a definite time (20 minutes) at room temperature. At the end of this time the reaction is stopped by precipitation of protein with trichloracetic acid. Aniline citrate is then added to decompose chemically the oxalacetate formed during the reaction to pyruvate. The pyruvate is converted to pyruvate dinitrophenyl hydrazone by addition of dinitrophenyl hydrazine. This is extracted with toluene, thus being separated from the excess reagent and the alpha-ketoglutarate hydrazone which may have been formed, since this latter is insoluble in toluene. The pyruvate dinitrophenyl hydrazone in the toluene layer is converted to a coloured compound by treatment with strong alkali in alcohol.

Transmittance at 490 millimicrons is determined with the blank set at 100% transmittance. (One unit is equal to

the activity by 1·0 millilitre of serum that results in the formation of chromogenic material equivalent to one microgramme of pyruvate under the conditions of the test—20 minutes at 26° C.)

The method uses inexpensive equipment and stable reagents, which are readily obtained. It is a comparatively speedy assay—approximately one hour is required for the estimation. However, it is not accurate at low levels. Deproteinization and toluene extraction present great difficulty. In the hot Queensland summer, unreliable results were obtained because of evaporation of toluene and alcohol. We abandoned the technique in favour of a more reliable colorimetric method.

The colorimetric method developed by Reitman and Frankel (1956) has not yet been published, but is described in detail in the Sigma Chemical Company's Technical Bulletin Number 505, of August, 1956. The basic steps in the estimation may be set out as follows:

1. Enzymatic conversion.

$$\text{Aspartate} + \alpha\text{-ketoglutarate} \xrightarrow{\text{S.G.O.-T.}} \text{oxaloacetate} + \text{glutamate}$$

Exactly 60 minutes' incubation of serum and substrate in a 37° C. (or 40° C.) water bath.

2. Formation of hydrazone.

Addition of "Sigma" colour reagent (acidified 2 : 4-dinitrophenylhydrazine) stops reaction and converts oxaloacetate→oxaloacetate hydrazone.

Leave exactly 20 minutes at room temperature (25° ±5° C.).

3. Formation of coloured compound.

Addition of 0·4N NaOH.

$$\text{Oxaloacetate dinitrophenylhydrazone} \xrightarrow{\text{0·4N NaOH}} \text{coloured compound.}$$

4. Estimation of depth of colour.

Exactly 30 minutes after addition of NaOH, read optical density at 505 mμ (any colorimeter with light filter in the range of 500–520 mμ may be used).

This method uses standardized reagents, and calibration of the colorimeter is required with each new batch of reagents.

The method has numerous advantages. No blank is required, there is no deproteinization and there is no extraction with toluene. Any good simple colorimeter with light filters in the range of 500 to 520 millimicrons can be used. It is speedy. The time for estimation is 110 minutes. The reagents require refrigeration only for stability. Values obtained by this method compare well with those obtained by the Karmen spectrophotometric method. We have used this method in approximately 400 assays, and have found it simple, quick and reliable, and the results readily reproducible.

## Results.

### Normal Values.

One hundred university students and laboratory personnel were used to establish a normal range for S.G.O.-T. activity using the Sigma-Frankel colorimetric method.

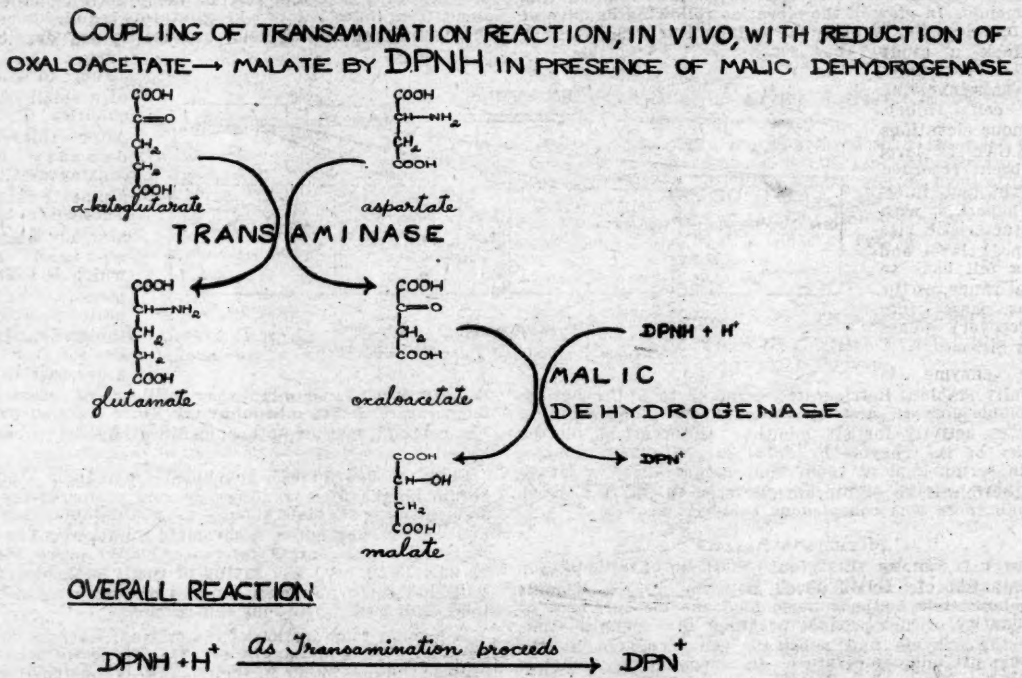


Figure III.

Reactions involved in the spectrophotometric assay of S.G.O.-T. activity.

Values ranged from six to 32 units, with mean activity of 14·0 units, and standard deviation of ±5·7 units. Repetition of the tests on normal subjects showed the results to be unaffected by age, sex, fasting state, previous muscular exercise, or physiological and minor pathological states.

All normal subjects were found to have the enzyme in the serum. The assay was not affected by the use of jaundiced serum. The only menace to its accurate study was hæmolysis, which caused misleadingly high values. Serum, and citrated, oxylated or heparinized plasma showed no difference in enzyme concentration. However, hæmolysed red blood cells have an enzyme concentration 10 times greater than that of serum or plasma. It is convenient that normal values obtained by the Sigma-Frankel method correspond well with the normal range obtained by the use of Karmen's spectrophotometric method. This means that all figures given for assays in the literature are comparable.

Karmen (1955) quoted normal values of nine to 36 units, with a mean of 19·6 units. Cabaud (1956), using his colorimetric method, found that 35 normal sera had a range of four to 40 units (mean 16·4 and standard deviation of ±8·4 units). In general, investigators regard values of five to 40 units as normal, 41 to 50 units as borderline and

greater than 50 units as high. This holds whether the units are Karmen's, Cabaud's or Sigma-Frankel.

### Miscellaneous Cases.

We found that the S.G.O.-T. level was not increased in patients suffering from infectious, neoplastic, degenerative, allergic, congenital, reactive and metabolic disease states, unless evidence of acute damage to liver, heart muscle or skeletal muscle had been present. All investigators confirm this, with the exception of two conditions—acute pancreatitis and some cardiac arrhythmias.

High levels of S.G.O.-T. in acute pancreatitis have been recorded for many cases. Chinsky *et alii* (1956) found a high incidence of increased S.G.O.-T. level. In 11 of 16 cases the values were high (greater than 50 units), in three they were borderline (41 to 50 units) and in two they were normal. The reason for this elevation remains to be investigated. In our only case of acute pancreatitis, the S.G.O.-T. level was 40 units 48 hours after the acute attack. Unfortunately, S.G.O.-T. estimation does not then provide the differential diagnosis between myocardial infarction and acute pancreatitis. A study of serum amylase is still required.

Chinsky (1956) also reported high S.G.O.-T. levels in some patients with cardiac arrhythmias when the ventricular rate was very high. Central lobular liver necrosis was cited as an explanation, as it was found at autopsy in one of these reported cases. Tachycardia produced by strenuous exercise in normal people does not alter the S.G.O.-T. level.

Table I shows some of the values we obtained in miscellaneous conditions.

### Heart Disease.

La Due, Wroblewski and Karmen (1954) described elevated S.G.O.-T. levels following myocardial infarction. Thirty patients all had serum levels of 100 to 6000 units on at least one of the five days following the onset of symptoms. In 22 subjects with heart disease uncomplicated by acute myocardial infarction, including arteriosclerotic heart disease associated with angina, coronary insufficiency, acute and chronic congestive heart failure, the S.G.O.-T. level was normal. They concluded that S.G.O.-T. activity rose within 12 to 24 hours in acute human myocardial infarction and returned to normal range within three to six days.

Agress *et alii* (1955) produced experimental myocardial infarction in dogs, by the method of coronary embolization with plastic microspheres. Serial samples of blood were taken from the time of infarction throughout the first 24 to 36 hours afterwards. The amount of infarction was estimated at autopsy in terms of percentage of the total myocardium. In all cases, S.G.O.-T. levels rose sharply after myocardial infarction. The results obtained by Agress and co-workers showed that there existed a relatively linear correlation between peak S.G.O.-T. levels and the amount of myocardial infarction as estimated at autopsy.

Wroblewski and La Due (1955a) obtained similar results showing a linear relationship between the peak S.G.O.-T. level and the percentage of myocardium infarcted, using experimental myocardial infarction in dogs. In addition, in 50 patients with transmural myocardial infarction the S.G.O.-T. level rose from two to 20 times the normal figure during the first three days.

Nydick *et alii* (1955) concluded, from experimental myocardial infarction in dogs, that the S.G.O.-T. level increased significantly after myocardial infarction, because S.G.O.-T. was released into the blood-stream as a result of an increase in permeability of the injured heart muscle cells.

Steinberg and Ostrow (1955) found that of 24 patients with electrocardiographic evidence of myocardial necrosis, only two showed normal S.G.O.-T. levels when samples were obtained within 48 hours after the onset of pain. Patients with transient myocardial ischæmia of *angina pectoris* without myocardial necrosis showed no elevation of S.G.O.-T. levels.

Chinsky *et alii* (1956) quoted 117 cases of acute myocardial infarction, in 84 of which there were typical electrocardiographic patterns and characteristic time-S.G.O.-T concentration changes. Of the entire 117 cases of diagnosed infarcts, 92% were associated with abnormally high S.G.O.-T. values. In those cases in which the S.G.O.-T. level was not raised, specimens could not be obtained at optimal times after infarction—either the patient died before the S.G.O.-T. level became elevated, or the first specimen was obtained after the S.G.O.-T. level had returned to its normal range. It was found that the optimal time for observing

TABLE I.

| Diagnosis or Circumstances.[1] | S.G.O.-T. Level. (Units.) |
|---|---|
| Acute myeloid leukæmia (2) | 17·5, 14 |
| Iron deficiency anæmia (1) | 23 |
| Hypoplastic anæmia (1) | 19 |
| Myeloma (2) | 24, 32 |
| Infectious mononucleosis (1) | 28 |
| Malignant hypertension (1) | 25 |
| Essential hypertension (1) | 10 |
| Rheumatoid arthritis (1) | 18 |
| Osteoarthritis (1) | 9 |
| Gout (3) | 11, 32, 19 |
| Gastric ulcer (1) | 18 |
| Duodenal ulcer (1) | 18 |
| Appendicitis (1) | 16 |
| Menorrhagia (2) | 14, 13 |
| Asthma (2) | 18, 12 |
| Hay fever (2) | 14, 18 |
| Chronic pancreatitis (1) | 22 |
| Acute pancreatitis (1) | 40 |
| Severe *diabetes mellitus* (3) | 18, 13, 20 |
| Hyperthyroidism (1) | 18 |
| Hypothyroidism (1) | 13 |
| Hypoparathyroidism (1) | 13 |
| Simmonds's disease (1) | 21 |
| Chronic congestive heart failure complicated by pyloric spasm (1) | 12 |
| Chronic nephritis (3) | 12, 14, 10 |
| Acute nephritis (1) | 12 |
| Potassium-losing nephritis (1) | 21 |
| Endometriosis (1) | 21 |
| Paralytic ileus (3) | 31, 33, 34 |
| Uncomplicated pregnancy (20) | 12–34 |
| Long-term anticoagulant therapy (10) | 10–34 |

[1] Figures in parentheses represent number of subjects.

the peak S.G.O.-T. level was 24 hours after the onset of acute pain. Patients with very high S.G.O.-T. levels were usually desperately ill, and had a high mortality rate. This was taken as evidence that very high S.G.O.-T. values following infarction may be a poor prognostic sign. Sixty-nine cases of anginal syndrome were also reported, and in no instance was a high level observed. Chinsky *et alii* quoted 16 cases of acute pulmonary œdema, 11 of chronic congestive heart failure, and five of benign idiopathic pericarditis, in which S.G.O.-T. values were also normal.

Kattus *et alii* (1956) cited 14 patients with a clear-cut diagnosis of acute myocardial infarction from clinical manifestations and electrocardiographic findings. The time-S.G.O.-T. concentration curves once again approximated those of Wroblewski and La Due. The peak S.G.O.-T. level was reached in most cases in less than 36 hours after the onset of the acute attack, and normal levels were generally reached by the fifth day. The S.G.O.-T. level reached its peak about two days before the maximum elevation in temperature, leucocyte count and erythrocyte sedimentation rate. Coronary insufficiency severe enough to produce marked *S-T* segment and *T* wave deviations in the electrocardiogram did not elevate the S.G.O.-T level.

Shabetai *et alii* (1956) also published results which confirmed the observations of Wroblewski and La Due.

In 13 cases associated with electrocardiographic and clinical findings typical of myocardial infarction, there were characteristic changes in S.G.O.-T. activity. In four cases, electrocardiographic findings were not helpful in making an early diagnosis, and clinical findings were atypical. All patients had raised S.G.O.-T. levels and were finally diagnosed on clinical and electrocardiographic findings as having myocardial infarcts. Twelve patients, suspected on clinical and electrocardiographic evidence of having sustained a myocardial infarction, all had normal S.G.O.-T.

activity. Follow-up investigation did not confirm the diagnosis. Final diagnoses of *angina pectoris* and coronary insufficiency were made in six cases. Thus the S.G.O.-T. result was confirmed again. The test found greatest applicability when myocardial infarction was suspected but could not be proved, and in cases in which infarction was not strongly suspected, but had to be excluded. The persistently negative results recorded in cases of *angina pectoris* were helpful in excluding myocardial infarction, especially when the electrocardiogram was difficult to interpret. We studied a series of 10 cases of suspected myocardial infarction, and obtained results similar to those quoted by previous workers. Typical time-S.G.O.-T. concentration curves were obtained during the five or six days following the infarction. Fig. IV shows one of the characteristic graphs obtained after acute myocardial infarction.

Mrs. A. was a middle-aged female with a classical clinical picture of myocardial infarction. Serial samples of venous blood were taken, the first specimen being withdrawn 17 hours after the acute onset of pain. The S.G.O.-T. level was found to be raised. The peak S.G.O.-T. activity of 125 units was reached at 20 hours, and normal levels were again obtained by the third day after the attack.

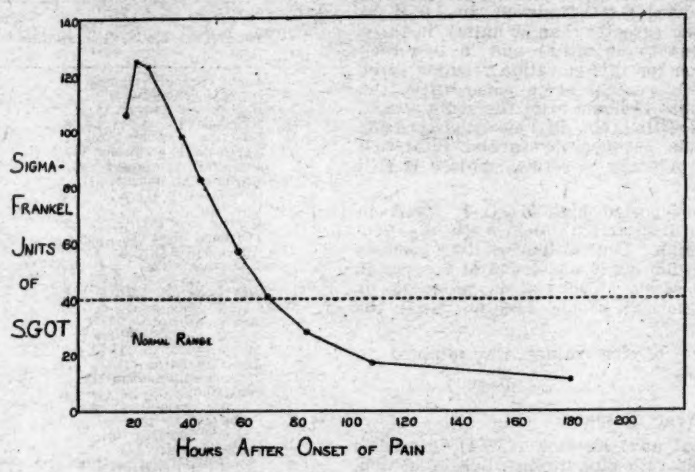


FIGURE IV.

This figure shows graphically serial changes in S.G.O.-T. level following the onset of pain in a typical case of acute myocardial infarction.

In another classical case of myocardial infarction, an increased S.G.O.-T. activity of 122 units was found 12 hours after the acute attack. When a further assay was made three days after the attack, the S.G.O.-T. level was within normal limits.

Very high levels of S.G.O.-T. are associated with a high mortality rate. In one case in which an assay was made six hours after the acute attack, the S.G.O.-T. activity was 42 units. By 18 hours, it had risen to 140 units, and at 22 hours it was 160 units. The level was high and probably still rising. The patient died at 66 hours after the onset of pain.

S.G.O.-T. assay was also shown to be valuable in excluding myocardial infarction.

Mr. B. was a middle-aged man, who had sustained a recent acute attack suspected of being acute myocardial infarction. S.G.O.-T. assay at 18, 36, 60, 84 and 156 hours failed to show increased S.G.O.-T. levels beyond normal values. The electrocardiographic findings were not typical of myocardial infarction.

*Comments.*

From a review of the work over the past three years, and from our own studies, it is possible to summarize the value of S.G.O.-T. estimation in the diagnosis of suspected myocardial infarction.

1. In myocardial infarction, S.G.O.-T. assay at 24 to 48 hours after the onset of pain gives valuable and early information which corrects and supplements the diagnostic inadequacies of the electrocardiogram, the erythrocyte sedimentation rate and the leucocyte count.

2. The transient myocardial ischæmia of *angina pectoris* is not accompanied by an elevation of the S.G.O.-T. level; thus serial S.G.O.-T. assays will differentiate myocardial infarction and angina when electrocardiographic evidence is not conclusive.

3. S.G.O.-T. values tend to be diagnostic of myocardial infarction before a definite electrocardiogram is available.

4. Elevated S.G.O.-T. values can be obtained in the presence of cardiac arrhythmias which would obscure characteristic electrocardiographic changes.

5. Elevated S.G.O.-T. values will clarify an electrocardiographic diagnostic problem when a left bundle branch block or the effects of digitalis obscure the tracing (Krause *et alii*, 1957).

6. S.G.O.-T. assays will help differentiate a recent myocardial infarct from acute pericarditis, and a recent infarct superimposed on an old one (Krause *et alii*, 1957).

7. S.G.O.-T. assays can aid the differential diagnosis between pulmonary thrombosis and myocardial infarction in cases of acute thoracic pain in the post-operative period. The S.G.O.-T. level is not increased in pulmonary thrombosis because of the low level of the enzyme in the lung.

8. The peak S.G.O.-T. value reached after infarction is roughly proportional to the size of the infarct. Serial assays will thus make it possible to gauge the amount of heart muscle damaged.

9. Very high S.G.O.-T levels following infarction are associated with a bad prognosis. A single S.G.O.-T. assay at the most opportune time following infarction — namely, 24 hours—can be very valuable; but because of the variable length of time at which peak S.G.O.-T. level is reached, it is advisable to make an assay every few hours (for example, at 12, 24, 36 and 72 hours), in case a single assay misses the rise in S.G.O.-T. level. Hergt and Langin (1957) described a classical acute myocardial infarct of 18 hours' duration, in which the S.G.O.-T. level was normal. The peak level was not reached till 42 hours after the onset of pain. Sampling more than three days after the acute episode is generally valueless, because the enzyme level will have fallen back to normal values. Maximal information is obtained by serial determination every 12 hours during the first two or three days after the onset of clinical symptoms.

### Liver Disease.

Acute hepatitis (toxic or infectious) is associated with a characteristic rise to a peak S.G.O.-T. activity and then a gradual fall to the normal range. Elevation of the S.G.O.-T. level precedes the onset of clinical symptoms, and the figure is abnormal before the results of conventional liver-function tests, such as estimation of serum bilirubin and serum alkaline phosphatase contents, thymol turbidity and cephalin flocculation are affected. Most patients are observed initially at the acute or recovery phase of the disease, and very high S.G.O.-T. levels are recorded. Levels of several hundreds or even thousands of units of S.G.O.-T. are seen in acute liver damage. Wroblewski and La Due (1955*b*) were the first to investigate the value of S.G.O.-T. estimations in diagnosis of liver disease. In their preliminary report they described tremendous elevations in acute liver-cell destruction due to carbon tetrachloride poisoning, with gradual return to normal values in a week, as the patient's clinical condition improved. Patients with infectious hepatitis and homologous serum jaundice also showed tremendous elevations of the S.G.O.-T. level, with gradual fall to normal during recovery. The results of other liver-function tests often remained abnormal for some time after the S.G.O.-T. level reached normal values.

Patients with metastatic carcinoma of the liver, cirrhosis and obstructive jaundice were also studied. It was concluded that an elevated S.G.O.-T. level indicated liver-cell destruction rather than liver-cell function.

Figure V shows S.G.O.-T. findings, together with the results of conventional liver function tests, in a case of homologous serum jaundice which we studied.

A female patient, aged 21 years, had 12 symptom days before we obtained our first specimen for assay. She had been admitted to hospital seven days previously, with vomiting, nausea, anorexia and jaundice of the conjunctiva. Blood samples were analysed every few days until S.G.O.-T. activity returned to the normal range. Initially, an S.G.O.-T. activity of 124 units was recorded, and the normal range was reached by the fourteenth day after admission to hospital. Thymol turbidity was still abnormal at this stage, but the level of alkaline phosphatase was almost in the normal range.

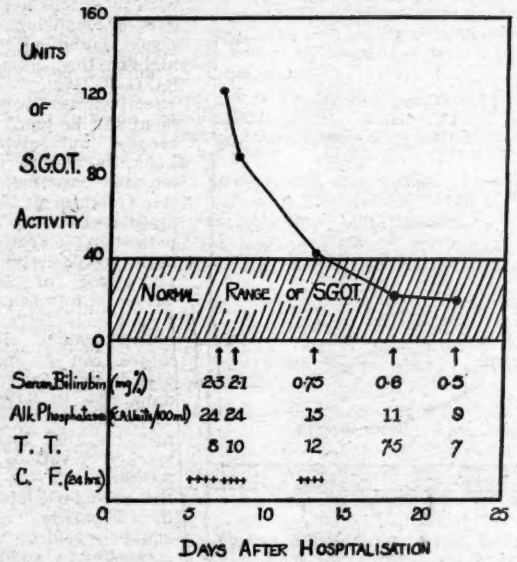
160
120
80
40
0
UNITS OF S.G.O.T. ACTIVITY
NORMAL RANGE OF SGOT
Serum Bilirubin (mg%) 2·5 2·1 0·75 0·6 0·5
Alk. Phosphatase (K.A. units/100 ml) 22 24 15 11 9
T. T. 8 10 12 7·5 7
C. F. (24 hrs) ++++ ++++ ++++
0 5 10 15 20 25
DAYS AFTER HOSPITALISATION

FIGURE V.

S.G.O.-T. level alterations, together with the results of the conventional liver function tests, during the recovery phase of homologous serum jaundice.

This patient was initially in the recovery phase of the disease, and the gradual fall of S.G.O.-T. level to normal shows the S.G.O.-T. alterations in the uncomplicated course of recovery in homologous serum jaundice.

Figure VI shows graphically the S.G.O.-T. alterations, together with the results of routine liver-function tests, during the course of infectious hepatitis.

A female patient, aged five years, had three days of symptoms—anorexia and upper abdominal pain—before the initial S.G.O.-T. assay. S.G.O.-T. determinations and liver-function tests were repeated every few days until the S.G.O.-T. level reached normal values. In the first specimen the level was 1080 units. By the thirteenth day after the patient's admission to hospital, the S.G.O.-T. level had reached normal values. The alkaline phosphatase level was still abnormal by the thirty-seventh day. Thymol turbidity and cephaline flocculation were also slower than S.G.O.-T. values in returning to normal.

Initially, we encountered the patient in the acute phase of the disease, and gradual return of S.G.O.-T. level to normal in 10 to 15 days is typical of the recovery phase of an uncomplicated case of acute viral hepatitis.

Figure VII shows the S.G.O.-T. changes in the course of a severe case of infectious hepatitis.

A female patient had 10 symptom days before the first specimen was taken. On the third symptom day, malaise, fever and severe jaundice were present. The patient had severe jaundice throughout the course of the disease. Initially the serum bilirubin level was 16·5 milligrammes per 100 millilitres, and it fell to normal values only by the sixty-fourth day after the patient's admission to hospital. S.G.O.-T. activity in the first specimen was 800 units. The level remained constantly about this value for 10 days, signifying unresolving hepatitis. Treatment gradually became effective, and the graph (Figure VII) shows a slow fall in S.G.O.-T. level to 100 units by the fifty-fifth day after the patient's admission to hospital. The S.G.O.-T. level was still outside the normal range when we discontinued estimations, but it was gradually falling towards normal range. When the S.G.O.-T. levels were highest, the patient's clinical condition was at its worst. As S.G.O.-T. levels decreased towards normal range, the patient's condition was also improving, showing a correlation between clinical status and S.G.O.-T. levels. The serum alkaline phosphatase content, initially 26 King-Armstrong units per 100 millilitres of serum, had fallen to 12 by the seventy-sixth day after the patient's admission to hospital. Thymol turbidity and cephalin flocculation were still abnormal.

This case demonstrates a typical course of S.G.O.-T. changes in a slow recovery from a severe attack of acute infectious hepatitis.

We encountered only one case of compensated cirrhosis of the liver. Normal levels were recorded in all assays, with only minimal daily fluctuations in activity.

In a case of active or uncompensated cirrhosis, the S.G.O.-T. activity was 80 units, which is in agreement with other recorded results.

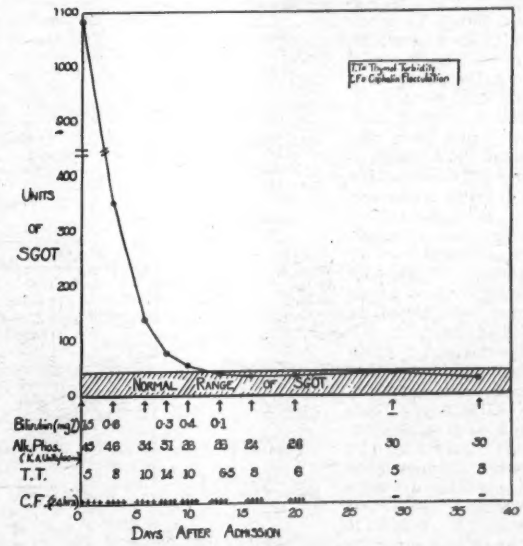


FIGURE VI.

S.G.O.-T. level alterations, together with the results of the conventional liver function tests, during the course of infectious hepatitis in a female patient, aged five years. The onset of clinical symptoms occurred three days prior to the initial assay.

### *Comments.*

From the literature and our own studies, it is possible to evaluate this test as a diagnostic aid in liver disease.

1. S.G.O.-T. estimations could prove valuable in the control of dosage of potentially hepatotoxic drugs. The S.G.O.-T. level is a sensitive and roughly proportional index of hepatocellular injury. The fact that increased S.G.O.-T. levels have been found to precede the development of jaundice resulting from chlorpromazine and pyrazinimide suggests that S.G.O.-T. estimations may be used to anticipate and thereby prevent toxic hepatitis in patients who are receiving potentially hepatotoxic drugs (Wroblewski and La Due, 1956). Wroblewski and La Due (1955*b*) found that acute toxic hepatitis due to carbon tetra-

chloride or drugs caused tremendous elevation of S.G.O.-T. levels (600 to 22,500 units), falling off to normal over five to ten days.

2. An increase in S.G.O.-T. level appears to be a relatively sensitive index of liver metastases. Wroblewski and La Due (1955*b*, 1956) found that 20 of 22 patients with proved liver metastases had increased S.G.O.-T. levels. Seven of these had no other signs of liver involvement. In their hands, S.G.O.-T. estimation proved very valuable for detecting metastatic carcinoma of the liver. In addition, the test has been useful in evaluating the significance of a raised serum alkaline phosphatase level, since the S.G.O.-T. level is normal when the phosphatase level is elevated as a result of bone disease or bone metastases. It is increased when alkaline phosphatase elevation is due to liver metastases.

3. Both acute and chronic hepatitis are associated with quantitative and serial elevations sufficiently characteristic to permit diagnostic differentiation. We have seen that acute hepatitis is associated with a characteristic rise to a peak S.G.O.-T. level and then a gradual fall to normal. Generally, only the peak and decline in S.G.O.-T. level are observed, as our graphs have shown. Very high activities of several hundreds or thousands of units are usual. Measurement of S.G.O.-T. levels during the acute phase of hepatitis usually permits differentiation of jaundice due to this cause from that due to cirrhosis, hepatoma or liver metastases. Cirrhosis when compensated is associated with normal levels of S.G.O.-T. When it is uncompensated or active, elevated S.G.O.-T. values of 40 to 300 units with daily fluctuations about a mean above the normal range are the finding (Wroblewski and La Due, 1956). Obstructive jaundice is characterized by S.G.O.-T. levels of 100 to 300 units, falling rapidly to normal when the obstruction is relieved (Wroblewski and La Due, 1955*b*, 1956). In primary hepatoma and metastatic carcinoma of the liver, generally there is a raised S.G.O.-T. level in the region of 45 to 250 units (Wroblewski and La Due, 1956). Thus, infectious hepatitis and homologous serum jaundice can be differentiated from obstructive jaundice if the S.G.O.-T. level is measured early and serially in the course of the disease. However, cases of cirrhosis or metastases in the liver cannot be separated from those of obstructive jaundice due to a stone in the common bile duct, for example, by a study of the S.G.O.-T. level alone. Hence S.G.O.-T. assay alone will not differentiate medical and surgical jaundice.

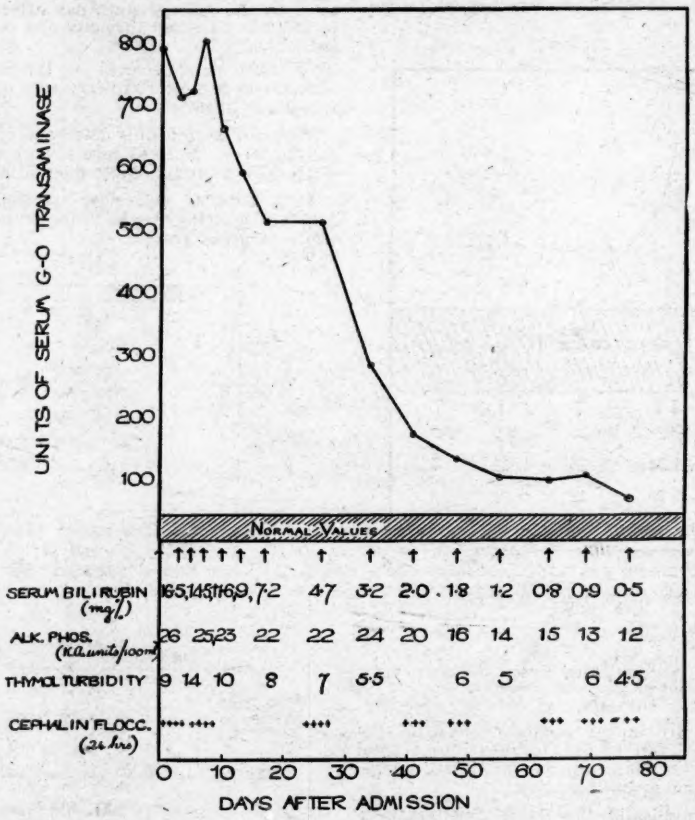
UNITS OF SERUM G-O TRANSAMINASE
800
700
600
500
400
300
200
100
NORMAL VALUES
SERUM BILIRUBIN (mg.%) 16.5 14.5 11.6 9.7 7.2 4.7 3.2 2.0 1.8 1.2 0.8 0.9 0.5
ALK. PHOS. (K.A. units/100ml) 26 25 23 22 22 24 20 16 14 15 13 12
THYMOL TURBIDITY 9 14 10 8 7 5.5 6 5 6 4.5
CEPHALIN FLOCC. (24 hrs)
0 10 20 30 40 50 60 70 80
DAYS AFTER ADMISSION

FIGURE VII.

S.G.O.-T. levels recorded during the course of a severe attack of infectious hepatitis. The patient had 10 days of symptoms before the initial S.G.O.-T. assay.

4. The subjective and objective clinical course of acute hepatitis appears to be accurately reflected in serial S.G.O.-T. alterations. Relapses, exacerbations, chronicity, premature ambulation and unrelated superimposed complications in cases of acute hepatitis are usually evidenced in variations from the usual pattern of serial S.G.O.-T. changes (Wroblewski and La Due, 1956). The S.G.O.-T. level correlates well with the clinical status. When the S.G.O.-T. level is increasing progressively, the clinical condition of the patient is worse. The intensity of signs and symptoms reaches a maximum when the peak level of S.G.O.-T. is reached. With fall in S.G.O.-T. values, patients are noticed to improve subjectively and objectively, although jaundice may still be present and the increase in serum bilirubin may not recede for several days. The more ill the patient with infectious hepatitis or homologous serum jaundice, the higher the peak S.G.O.-T. level. The effectiveness of treatment can be gauged, because unresolving hepatitis due to inadequate or ineffective treatment is associated with a persistent elevation of S.G.O.-T. activity, instead of the characteristic gradual fall to normal range. Relapses can be predicted by a secondary rise in S.G.O.-T. level. Wroblewski and La Due found marked elevations of S.G.O.-T. activity in the pre-icteric stage of hepatitis and could predict relapses by a sudden rise in the S.G.O.-T. level of patients with hepatitis clinically considered to be convalescent. The correct time for ambulation can be told, and premature ambulation, which would result in relapse, can be detected and the relapse prevented. If on ambulation the S.G.O.-T. level rises by 50 or more units, a return to rest discipline is advisable, and S.G.O.-T. activity usually resumes its return to normal. It is of note that the results of other liver function tests are usually abnormal for days or weeks after S.G.O.-T. activity has returned to normal. The failure of S.G.O.-T. activity to return to normal suggests the development of chronic hepatitis and/or post-infectious cirrhosis. A persistent elevation of S.G.O.-T. level has been associated with a poor prognosis in the cases that have been observed.

5. Wroblewski and La Due (1956) have worked on epidemiological considerations. Elevation of S.G.O.-T. levels above normal range in the asymptomatic and/or prodromal phase permitted ready detection of acute hepatitis. Their results suggested that S.G.O.-T. investigation of all contacts during an epidemic would permit differentiation of those who may develop non-icteric,

subicteric and/or frankly icteric infectious hepatitis from those who will remain normal. They suggested that the former group could then be prophylactically treated with immune globulin, without its being administered to the larger group with normal S.G.O.-T. levels who are not potential subjects of subclinical and clinical hepatitis. The possibility that isolation of individuals with abnormal S.G.O.-T. levels during an epidemic would stop dissemination of the disease remains to be tested.


## SUMMARY.

1. Various methods of S.G.O.-T. assay are reviewed.

2. One hundred young adults were used to establish a normal range for S.G.O.-T. activity by means of the Sigma-Frankel colorimetric method. Activities ranged from six to 32 units, with a mean activity of 14 units and standard deviation of ±5·7 units.

3. S.G.O.-T. levels in various disease states not involving acute damage of heart muscle, skeletal muscle or liver tissue were found to be within the normal range of activity, with the exception of acute pancreatitis, which was associated with an increased level.

4. The S.G.O.-T. level rose to two to 20 times the normal level within 12 to 24 hours after acute myocardial infarction, and returned to the normal range within three to seven days.

5. Four of our cases of suspected myocardial infarction have been quoted, together with the results obtained in various cardiac conditions by several investigators.

6. An evaluation of the level of S.G.O.-T. activity as a diagnostic tool in suspected myocardial infarction has been given.

7. The importance of careful consideration of the time relationship between onset of symptoms and performance of the test has been emphasized. Serial assays every few hours (for example, 12 hours) for the first two or three days give maximal information.

8. Serial S.G.O.-T. alterations in three cases of homologous serum jaundice and infectious hepatitis have been described graphically, together with the clinical picture during the course of the disease.

9. The value of S.G.O.-T. determinations in hepatic disease has been stated.

10. Epidemiological problems have been briefly considered with regard to the use of the estimation in the control of endemic and epidemic viral hepatitis.


## CONCLUSIONS.

The estimation of the S.G.O.-T. level supplements the electrocardiogram as a diagnostic aid.

S.G.O.-T. determination is of great value in cases of suspected myocardial infarction which cannot be confirmed electrocardiographically, and when myocardial infarction has to be excluded. The peak S.G.O.-T. level provides a roughly quantitative estimate of the amount of myocardium involved, and has prognostic significance.

Serial S.G.O.-T. estimations are valuable in the differential diagnosis of acute and chronic hepatic disease, and in the management of acute hepatitis, with regard to the effectiveness of treatment, the correct time for ambulation, the detection of relapses before the onset of clinical symptoms, and the prognosis.

Other possible uses, as a sensitive index of liver cell injury, are (*a*) for the control of the dosage of potentially hepatotoxic drugs and (*b*) for the control of endemic and epidemic hepatitis.

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# Reviews.

**Cerebral Lipidoses: A Symposium.** Edited by J. N. Cumings, M.D., F.R.C.P., and A. Lowenthal, M.D.; Chairman, L. van Bogaert, M.D.; 1957. Oxford: Blackwell Scientific Publications. 9″ × 5½″, pp. 214, with illustrations. Price: 42s. (English).

IN July, 1955, a symposium devoted to the study of cerebral lipidoses and leucodystrophies was held in Antwerp under the auspices of the Inter-University Foundation of Neuropathological Research. In his introduction to the proceedings, L. van Bogaert states the objectives of the colloquium to be, first, the classification of the various lipid disorders and their interrelationships, secondly, assessment of the value of histochemistry, and thirdly, comparison of the quantitative chemical methods used in different laboratories.

The fact that all substances accumulating in the lipidoses are constituents of normal axons and the myelin sheaths surrounding them is the link between the lipidoses and the leucodystrophies. This fact also contributes to the confusion in the histochemical study of these disorders. Nevertheless, it is clear that classification of the leucodystrophies depends upon histochemistry, whereas the thesauroses can often be identified by ordinary histological techniques. Quantitative chemistry is, as yet, a research method with little routine diagnostic value.

There is little in this symposium for the average clinician unless he is particularly laboratory-minded. For the pathologist, on the other hand, this book is invaluable. The methods by which one identifies the various disorders are collected together in one volume and critically appraised by the world's experts. The illustrations are good, and when necessary coloured photomicrographs illustrate the histochemical techniques. This symposium fulfils a long-felt need and should be found in every pathology department.

**Laboratory Applications in Clinical Pediatrics.** By Irving J. Wolman, M.D.; 1957. New York, Toronto and London: The Blakiston Division, McGraw-Hill Book Company, Incorporated. 9" x 6", pp. 1032. Price: $15.00.

THERE are a number of books available, the purpose of which is to assist the practitioner to make the best use of the laboratory facilities available to him. These publications touch slightly or not at all on pædiatric medicine, and this has left a serious deficiency waiting to be filled. Dr. Wolman has set out to repair this omission, and is therefore catering for a demand which must be considerable.

His book covers all aspects of laboratory work except tissue pathology, and is directed to students, residents and clinicians who are not attached to large pædiatric units. Since the range of readers aimed at is so wide, it is inevitable that much material will be included which, to the experienced, will be self-evident. Readers versed in pædiatric pathology must therefore expect some tedium, but this is not too high a price to pay, since a careful reading will disclose many facts of much value. Those who are responsible for the running of pædiatric laboratories should have this book, if for no other purpose than to help in convincing their sceptical clinical colleagues, particularly with regard to variations arising from a labile physiology—variations which are often accredited to an unstable technique.

Illustrations are completely lacking, nor are there any charts or diagrams. A few well-chosen illustrations might usefully replace some of the lengthy descriptions, especially of abnormal varieties of blood cells. Further, except when these cells differ from similar cells encountered at other ages, no detailed description would appear necessary. Exception is also taken to the use of the term "megaloblast" for a normal immature red blood cell, and the use of the terms "rubriblast", "megaloblast", and "normoblast" to indicate a nucleated red blood cell of increasing maturity is unorthodox and confusing. The final chapter on poisons might well be enlarged.

These are minor criticisms and detract from the worth of the book perhaps only to ourselves. We nevertheless remain convinced that this is a most useful addition to the medical literature. Moreover, its value should extend beyond the audience claimed for it, and it should prove of considerable value to experienced pædiatricians, whether their work is in the wards or in the laboratories, always provided that they are prepared to search for what is, for them, the substance.

## Books Received.

*[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]*

"General Diagnosis and Therapy of Skin Diseases: An Introduction to Dermatology for Students and Physicians", by Hermann Werner Siemens, M.D.; 1958. Chicago: The University of Chicago Press. 9½" x 6½", pp. 236, with 375 illustrations. Price: $10.00.

The author is Professor of Skin and Venereal Diseases at the University of Leiden, Holland.

"The Medical Clinics of North America, November, 1957: Gastroenterology." Guest editor, Henry L. Bockus, M.D. 1957. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 9" x 5½", with illustrations. Price (six issues per year): £8 2s. 6d. (cloth binding), £6 15s. (paper binding).

Contains a symposium on gastro-enterology from faculty members of the University of Pennsylvania Graduate School of Medicine together with a number of distinguished guest speakers. Included are three unrehearsed panel discussions on peptic ulcer, the malabsorption syndrome and diseases of the liver.

"Biochemistry and Human Metabolism", by Burnham S. Walker, M.D., Ph.D., William C. Boyd, Ph.D., and Isaac Asimov, Ph.D., Third Edition; 1957. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9" x 6", pp. 944, with illustrations. Price: £6 12s.

Fully revised since the previous edition was published in 1954.

"Headache: Diagnosis and Treatment", by Robert Ryan, B.S., M.D., M.S., F.A.C.S.; Second Edition; 1957. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical), Limited. 8½" x 5½", pp. 424. Price: £3 14s. 3d.

The author is an otolaryngologist, but the book is intended to appeal to those in all fields of medicine.

"Variation and Heredity", by H. Kalmus, M.D., Sc.D.; 1958. London: Routledge and Kegan Paul, Limited. Sydney: Walter Standish and Sons. 8½" x 5½", pp. 234, with many illustrations. Price: 28s. (English).

Deals with "the inequality of man" and its genetical and environmental causes.

"Recent Advances in Obstetrics and Gynæcology", by Aleck W. Bourne, M.A., M.B., B.Ch., F.R.C.S., F.R.C.O.G., and Leslie H. Williams, M.D., M.S., F.R.C.S., F.R.C.O.G.; Ninth Edition; 1958. London: J. and A. Churchill, Limited. 8" x 5", pp. 356, with 78 illustrations. Price: 38s. (English).

The previous edition was published in 1953.

"Noise and Your Ear", by Aram Glorig, jnr., M.D.; 1958. New York, London: Grune and Stratton. 8½" x 5", pp. 160, with illustrations. Price: $6.50.

A survey of existing information about hearing loss and noise. It is not an exhaustive treatise and is not intended for the expert.

"The Functional Organization of the Diencephalon", by W. R. Hess; edited by John R. Hughes, M.A., Ph.D.; 1957. New York, London: Grune and Stratton. 8½" x 5", pp. 192, with many illustrations. Price: $7.00.

The author is Professor of Physiology, Emeritus, in the University of Zurich, and a Nobel Prize winner. This edition is a translation of his book *"Das Zwischenhirn"*.

"The Story of Peptic Ulcer", conceived by Richard D. Tonkin, M.D., F.R.C.P., characterized by Raymond Keith Hellier, F.R.S.A.; 1957. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 5¼" x 7½", pp. 80, with many illustrations. Price: 22s. 6d.

A humorous illustrated book to guide the ulcer patient.

"Growing Up", by Karl de Schweinitz; Second Revised Australian Edition; 1957. Australia: Father and Son Welfare Movement of Australia. 7½" x 5", pp. 86, with 32 illustrations. Price not stated.

A book for boys and girls of school age about the reproduction, birth and growth of human beings and of animals.

"Pædiatrics for Nurses", by Arthur G. Watkins, M.D., F.R.C.P.; Second Edition; 1958. Bristol: John Wright and Sons, Limited. 7¼" x 4¾", pp. 208, with many illustrations. Price: 15s. (abroad).

Fully revised since the previous edition of 1947.

"The Relation of Psychiatry to Pharmacology", by Abraham Wikler, M.D.; 1957. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 10" x 6¾", pp. 334, with no illustrations. Price: 44s.

A comprehensive survey of the recent literature.

"The Year Book of Radiology" (1957-1958 Year Book Series). Radiologic Diagnosis, edited by John Floyd Holt, M.D., and Fred Jenner Hodges, M.D.; Radiation Therapy, edited by Harold W. Jacox, M.D., and Morton M. Kligerman, M.D. Chicago: The Year Book Publishers, Inc. 9" x 5¾", pp. 148, with 335 illustrations. Price: $10.00.

One of the Practical Medicine Series of Year Books.

"Clinical Neurosurgery: Proceedings of the Congress of Neurological Surgeons, 1956"; 1957. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9" x 5¾", pp. 147, with many illustrations. Price: 77s.

Contains eight papers presented at the Congress of Neurological Surgeons held in Chicago in 1956. Seven of the papers deal with various neurological aspects of the pituitary region.

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## MEDICAL EDUCATION: A RETROSPECT.

It is not such a very long time ago since the question of medical education was treated with scant attention by public authorities, private citizens or even members of the medical profession itself. Perhaps the one exception to this seeming indifference might arise in the case of a conscientious parent faced with a grave economic problem when one of his sons showed a determination to undertake the necessary training required for a medical career. In England towards the end of the eighteenth century, in order to reach the heights as a Fellow of the Royal College of Physicians, it was necessary to spend 14 unproductive years at Oxford or Cambridge University acquiring a broad general culture based on a knowledge of the dead languages, followed by several years devoted to the study of medical treatises handed down from the ancients to an appreciative posterity. More commonly, financial embarrassments left the parent no alternative but to apprentice his son to an apothecary or surgeon, and the son no alternative but to accept the inferior status accorded by the community to this type of practitioner. In any event, all ranks of the profession entered the arena of medical practice to find themselves in keen competition with a host of quacks and charlatans, who were permitted to batten freely on the ignorance and credulity of an indifferent public.

All this time people were slow to realize that their world was already in the process of a radical change, as new discoveries and inventions in science and industry began to have a disturbing impact on the even tenor of everyday life. However, a few enlightened enthusiasts with advanced ideas and a progressive attitude toward the future were convinced that the old order was fast becoming obsolete, and that active steps must be taken to meet a new challenge. In England, open revolutions have never been a popular pastime; so deeply entrenched was the respect for tradition and established precedent that any attempt to bring about reform was met by a formidable array of organized opposition. But with the passage of time the masses were noticeably less ignorant and poverty-stricken than they used to be; politicians were more sensitive to the intricacies of public opinion; and the gradual diffusion of a more rational and scientific outlook began to stir up undercurrents of dissatisfaction with the old systems of medical education and private practice.

The unintentional assistance given in earlier days by the older teaching institutions in England to the encouragement of modern trends in medical education is seldom given the emphasis it deserves. Their intransigence in refusing to admit all students who were unwilling to subscribe to the thirty-nine Articles of the Church of England, the Established Church, gave impetus to a new phase of learning, by reason of the fact that nonconformists were obliged to establish schools of their own where modern languages, general science and mathematics were at once given a prominent place in the curricula. The same movement culminated in the foundation of a non-sectarian university in London, at first represented by University College, which soon built its own teaching hospital; there the Quaker, Joseph Lister, could find a spiritual home as a medical undergraduate and be trained in all the latest methods of scientific and clinical medicine.

At the dawn of the nineteenth century the question of medical education began seriously to exercise the minds of a number of responsible people, both within and outside the profession. In his recent book on "The Evolution of Medical Education in the Nineteenth century", Professor Charles Newman,[1] Dean of the Postgraduate Medical School of London, admirably summarizes the difficulties encountered by the diverse medical corporations in their efforts to placate petulant public opinions, and to rectify certain anomalies of a purely domestic nature which had arisen out of professional jealousies, a devotion to the idols of vested interest, and a determination to retain at all costs established privileges which had been sanctioned and enjoyed for ages past. The medical corporations most concerned in countering threats to their traditional customs and beliefs were the Society of Apothecaries, the Royal College of Surgeons in London and the Royal College of Physicians, which remained firmly resistant to any public interference with their own private affairs.

Professor Newman deals exhaustively with all aspects of the professional, academic and political moves and countermoves before and after the passing of the *Apothecaries' Act* of 1815, when the Royal Colleges were completely sidestepped through their determination to oppose vigorously any honest parliamentary effort to have organized and placed on a proper basis the education, training and legal status of a reasonably safe and competent general practitioner. It is clearly indicated in the course of the narrative that the profession had lost its sense of proportion, and no little of its former dignity, in refusing to recognize an important sign of the times. Rational medicine was being fortified by new methods of physical diagnosis imported from the Continent, the microscope had been converted into an instrument of efficiency, while the studies of clinical pathology, histology and hæmatology were already widening horizons in enlightened medical thought.

It is indeed a pathetic commentary on the conservatism of last century that the profession had to be welded into some semblance of homogeneity by outside pressure from Members of Parliament, and the general public and, not the least disconcerting, by the caustic diatribes of the

[1] "The Evolution of Medical Education in the Nineteenth Century", by Charles Newman, M.D., F.R.C.P.; 1957. London, New York, Toronto: Oxford University Press. 8½" × 5½", pp. 352. Price: 30s. (English).

editor and founder of the first English medical publication, *The Lancet* (1823). While still conducting a ruthless campaign from his editorial chair, the ebullient Dr. Thomas Wakeley conceived the idea of strengthening his strategic position by winning election to a seat in Parliament, where he set out to convince the House of Commons and the general public, as well as a few obstructionists in the Royal Colleges, that medical reform was not only imperative but inevitable in the near future.

Until the first *Medical Act* received the royal assent in August, 1858, the profession had been divided and embittered by sectional interests; the teaching of students had been haphazard and uncoordinated; and there were at least 17 independent bodies concerned with the examination and qualification of candidates for medical diplomas. In actual fact, "it was the student's duty to get his education, not that of the teacher to give it". Professor Newman gives chapter and verse for all the different amendments to the original *Medical Act*, spread out over the second half of the century, as continuing changes and fresh scientific knowledge slowly brought about a more reasonable attitude to radical suggestions for reform. Here and there we find a statement bearing on the new concepts expressed clearly in epigrammatical form. For example: "A student's time for the entire course is his own property, to use and organize as he chooses. This is at once his freedom and his responsibility. It is also a part, and a most valuable part, of the educational process. It is on his success in learning to do this that his power to educate himself, when he has left all school and university props behind, will depend." And again: "The main difficulty in medical education is not what to teach or how to teach it, but to make up one's mind exactly what one is trying to produce."

Towards the end of the book there are interesting and instructive commentaries on the value of a university education, the rise of laboratory medicine and the medical education of women. It is assumed from the remarks of Professor Newman that he is partial to simplification and uniformity in medical education—which term has a Latin derivation meaning "to lead something out" of a medical student rather than to cram something into him. Newman infers that true education is well served in the healthy atmosphere of a university, where is to be found "a society devoting itself to the advancement and diffusion of knowledge and of the spirit of inquiry in as many subjects as possible, gathered together in one place". And he goes on to say: "In so far as a university happens to stand, in time, between school and the business of life, it is also part of its duty to train the young towards an adult, sensible, independent, responsible mentality; to teach schoolboys to drink and smoke, as the old derisory criticism had it, a criticism which is, in truth, a great compliment to universities."

There is still a considerable body of opinion among educationists that the finest qualities of heart and mind can best be encouraged to reach florescence in the undergraduate who is fortunate enough to be brought into a kind of spiritual union with the academic, cultural, disciplinary and social influences of a great university. Professor Newman is obviously very much in sympathy with that opinion, and it would be a grave mistake to treat it lightly in planning the major developments now envisaged in medical education in Australia.

# Current Comment.

## THE INFECTIOUSNESS OF HUMAN TUBERCULOSIS.

"Epidemiology", writes J. N. Morris, in discussing the uses of this discipline,[1] "supplements the clinical picture, by setting clinical problems in community perspective, by indicating their dimensions and distribution, and where action is needed."

In a meticulous study of the infectiousness of human tuberculosis, G. Hertzberg[2] has used the epidemiological method to investigate the effect of a variety of findings in tuberculous patients on the proportion of their household contacts who become infected and who develop tuberculous disease. The findings with regard to spread of infection to household contacts are exactly as one might expect. Patients whose sputum always contains tubercle bacilli on direct smear examination are shown to be twice as infectious as those whose sputum is "negative" on smear examination, but "positive" on culture. The patient with positive findings on direct smear examination of the sputum is four times as infectious as the patient from whom organisms can be recovered only by culture of gastric content or material from a laryngeal swab, and about ten times as infectious as the tuberculous patient from whom organisms cannot be recovered. It is also not surprising to learn that patients in whose discharges tubercle bacilli can be demonstrated constantly are twice as infectious as those in whose discharges organisms are found only intermittently, and that those whose cultures produce large numbers of colonies are more infectious than those whose cultures produce but few colonies. Perhaps more striking is the demonstration that "culture-positive" patients who have cough and sputum infect six times as many of their household contacts as do "culture-positive" patients who have no cough or sputum. Hertzberg also shows that patients with cavitary disease are considerably more infectious than those without detectable cavities, even though the bacteriological findings are indistinguishable.

The findings with regard to tuberculous disease as distinct from mere infection among the contacts are more interesting, because they follow less closely what one might have predicted. In his discussion of tuberculous disease among contacts, Hertzberg distinguishes between Morbidity I, which is the proportion of all contacts manifesting active tuberculosis, and Morbidity II, which is the proportion having active tuberculosis among those contacts who react to tuberculin. In other words, Morbidity I is the disease attack rate among all contacts, and Morbidity II is the disease attack rate among infected contacts. Perhaps the most striking observation recorded is that, while infection among the contacts is ten times more frequent if the patient who is the source of the infection has "positive" sputum on direct smear examination than if organisms cannot be found, tuberculous disease among the contacts is under these circumstances 28 times more frequent. Small differences in numbers of bacilli eliminated by patients who are sources of infection are associated with quite marked differences in infection rates in household contacts; but only large differences in numbers of bacilli eliminated are reflected in differences in contact morbidity. When these differences in morbidity do show up, they are strikingly large. Cough and sputum are shown to have almost as great an effect on the disease attack rate as they have on the infection rate within the home. Cavitary disease is also shown to have a very important influence on the disease attack rate. It is interesting to note that patients with renal, bone and joint, and lymph gland tuberculosis are apparently all able to infect a proportion of their contacts, though there was no case of manifest tuberculosis among the 95 contacts of patients of these types.

[1] *Brit. M. J.*, 1955, 2: 395 (August 13).

[2] "The Infectiousness of Human Tuberculosis: An Epidemiological Investigation", by Gerh. Hertzberg; *Acta Tuberculosea Scandinavica*, Supplement XXXVIII, 1957. Copenhagen: Einar Munksgaard. 9¾" × 6¾", pp. 146.

The group studied comprised 2361 new tuberculous patients in Oslo in the 14 years from 1940 to 1953, and their 9611 household contacts. It is noteworthy that every one of the household contacts was examined. Hertzberg realizes that the differences in morbidity which he has observed in his various groups of contacts may be open to several explanations. While he is most impressed with the importance of actual numbers of tubercle bacilli in the environment, he draws attention to the fact that household contacts are likely to be genetically similar material to the sources of infection, and that therefore contacts of infection sources who have reacted unfavourably to the tubercle bacillus would themselves be likely to react unfavourably for genetic reasons. The importance of both these effects has been amply demonstrated by M. B. Lurie, A. G. Heppleston, S. Abramson and I. B. Swartz[1] in experimental animals. The third possibility, that different strains of tubercle bacilli may differ markedly in virulence, is mentioned, but discarded as being unlikely, unsupported by animal experiment, and in any event not susceptible of investigation in man.

The value of this investigation is threefold: it confirms widely held views on the relative importance from the public health viewpoint of different types of tuberculous patients; it demonstrates the importance and the danger of symptoms in pulmonary tuberculosis, and therefore indirectly the value of early case-finding by survey methods; and it shows unmistakably not only that the eliminator of large numbers of tubercle bacilli infects a large proportion of his immediate contacts, but that probably by sheer weight of numbers of organisms, a surprisingly large proportion of these infected contacts are found to have manifest tuberculosis.

## PERINATAL MORTALITY.

THE most dangerous period in the life of the infant is that immediately before, during and after birth. The closer the time of delivery, the greater the danger to the infant. According to a recently published study by the World Health Organization (WHO),[2] this is becoming more and more apparent because of the fact that while infant mortality generally has decreased sharply, mortality at birth has decreased much less. In England and Wales, for example, mortality among infants between six and twelve months of age has dropped 92% since the beginning of the century, but the decrease of mortality among infants immediately after birth is only about one-third of that. The loss of life at birth, therefore, accounts for an increasing percentage of infant mortality.

To further understanding of this, as yet, inadequately explored phase of human mortality, the specialists have introduced a new concept, perinatal mortality, covering the period from the twenty-eighth week (seventh month) of pregnancy to the first week of life, and the WHO study represents an initial attempt to collect international statistics concerning this period. It shows that almost a third of all perinatal deaths occur on the day of birth, that the death rate is considerably higher for boys than for girls, but that far more girls than boys die of congenital malformations of the nervous system. The reasons why this is so are not yet clear, and the fact that a high percentage of perinatal deaths are listed in the study as being due to "ill-defined or unspecified causes" also goes to show that much has yet to be learned about perinatal mortality. Deaths due to conditions of the fœtus itself account for the highest percentage of perinatal mortality; in Canada, for example, the percentage is 45·7. Next come obstetrical causes (31%), then congenital malformations (14·8%), and, finally, "causes in mother", accounting for 8·5% of all perinatal deaths.

What are the prospects of controlling these causes? The drop in infant mortality generally is, first of all, a result of immunization against communicable diseases and a decline in gastro-intestinal diseases due to the education of mothers and the efforts of well-baby clinics. With the scientific knowledge available, a further lowering of perinatal mortality is still possible, both in regard to these conditions and in regard to those affecting the infant before as well as after birth, such as syphilis and infectious diseases like rubella and chickenpox, which, apparently, are mild to the expectant mother, but nevertheless a cause of congenital defects in her baby. To prevent these diseases from damaging the baby, action must be taken before birth—indeed, many years before, if, for example, rickets in the mother, which is a cause of death to the infant during delivery, is to be checked.

Of the 17 countries covered by the study, Norway has the lowest perinatal mortality, with 26 deaths in 1955 per 1000 live births, followed by New Zealand (28), Sweden (28·4), the Netherlands (29·2), United States of America (30·4), Switzerland (30·9), Canada (31·5), Finland (33·6), Denmark (33·9), France (34), Belgium (35·4), England and Wales (38·3), Austria (40·5), Scotland (42·1), Gemany, Federal Republic (44) and Italy (46·2). The study warns, however, that the collection of statistics on perinatal mortality is still difficult in many countries, and that the imperfect nature of the data should be borne in mind when numerical comparisons between countries are made.

## RECRUDESCENCE OF SYPHILIS.

LEAVING out the war years, which do not lend themselves to statistical treatment, we find good evidence that syphilis declined steadily throughout the world until 1954, a matter for gratification to all citizens of the time. A. Touraine,[1] of Paris, after a laborious survey of the subject, not only in France but in all countries from which reliable statistics can be obtained, has come to the definite conclusion that a recrudescence of this plague began in 1955 and may continue. The figures for syphilitic infestation given by Touraine are interesting and occasionally startling. Whilst most civilized countries show roughly 6% to 9% of the population affected, there are foci of the disease which manifest higher grades of infection. Thus Saudi Arabia has 20·4% of men and 27% of women, Bechuanaland 22% of the population, Southern Rhodesia 14% to 33%, and Basutoland 29%. Touraine does not mention that the Negro seems prone to contract the disease. The surprisingly high incidence of venereal infection amongst United States servicemen when resident in Australia was commented on in these columns on a previous occasion, and the coloured population of North America south of Canada was mentioned as a possible cause. Touraine discusses the various factors which could bring about this unexpected revival. He holds the view, which he shares with many others, that economic prosperity leads to venereal expansion, for an increase in prostitution follows increased income. The exploitation of oil in Saudi Arabia may be the cause of the high figure given for syphilis. Travel is more rapid, and an ever greater percentage of population today resorts to travel; a venereal focus on an air route halt can lead to a spread of infection. The decline in virulence and in the number of persons affected, together with improved methods of treatment, has led to the medical profession being less alert to the danger and to a lowered standard of education on the subject amongst medical students. Touraine is convinced that clandestine prostitution is a big favouring factor. He might have here added that many Americans believe that rigorous police suppression of prostitution in cities has favoured this clandestine element; this, however, is matter for debate. Touraine suggests a greater emphasis on the study of venereal disease in medical schools and an extension and deepening of sex education in non-medical citizens.

[1] *Am. Rev. Tubere.*, 1950, 61: 765.

[2] *Epidemiological and Vital Statistics Report*, Vol. 10, No. 11-12, 1957.

[1] *Presse méd.*, November 16, 1957, page 1851.

# Abstracts from Medical Literature.

## NEUROLOGY AND PSYCHIATRY.

### The Limp Child.

J. N. WALTON (*J. Neurol., Neurosurg. & Psychiat.*, May, 1957), under the heading "The Limp Child", discusses 17 out of 109 cases in which a diagnosis of *amyotonia congenita* has been made and the patients followed up. These 17 patients were all diagnosed as suffering from *amyotonia congenita* in infancy because of generalized hypotonia and weakness of the skeletal muscles, increased range of passive movements at the joints and delay in physical development. Eight of these patients recovered completely at some time between the fifth and fifteenth year of life, while the other nine improved to some extent, but have shown evidence of persisting muscular disability throughout life. The author has called these cases "benign congenital hypotonia". Electrical testing of affected muscles gave no evidence of disease in the peripheral nerves. He suggests that it is a distinctive syndrome which may result from a congenital neuro-muscular abnormality of varying severity. Thus not all patients with the clinical picture of *amyotonia congenita* ("the syndrome of the limp child") have a gloomy prognosis.

### Rathke's Pouch Tumours.

D. W. C. NORTHFIELD (*Brain*, September, 1957) reviews the cases of 49 patients with Rathke's pouch tumours. The patients usually presented with symptoms of raised intracranial pressure or interference with vision. The signs were of endocrine disturbance, defects of visual fields and papilloedema or optic atrophy. The author suggests that the mechanism whereby these tumours interfere with hypophyseal functions is by interference with the hypophyseal portal system. He advocates a conservative surgical approach, reserving radical operations for intrasellar and subtuberal tumours. These tumours grow slowly and in an unpredictable manner. Some tumours are compatible with near normal life, provided obstructive hydrocephalus can be relieved. He regards the tuberal or intrinsic tumour as irremovable and prefers to relieve obstructive hydrocephalus by a ventriculo-cisternostomy.

### Arteriovenous Malformations of the Brain.

J. CARRASCO-ZANINI (*J. Neurol., Neurosurg. & Psychiat.*, November, 1957) studied 102 patients with cerebral arteriovenous malformations, from the Radiological Department, Queen Square, London, in order to assess the influence of these anomalies upon the rest of the cerebral circulation, and analysed the X-ray changes after the surgical extirpation of the lesion in 15 of these patients. The afferent artery was consistently found to be dilated, as well as arteries feeding adjacent territories, and even the common carotid and vertebral arteries. This secondary arterial dilatation disappeared after removal of the angioma and a marked improvement of circulation was seen in previously unfilled arteries, especially the anterior cerebral artery when the angioma was in the territory of the middle cerebral artery.

### A Familial Brain Lesion.

R. J. STROBOS, E. DE LA TORRE AND J. F. MARTIN (*Brain*, September, 1957) describe symmetrical calcification of the basal ganglia with familial ataxia and pigmentary macular degeneration. The symmetrical calcification of the basal ganglia was identified in X-rays of the skull in two brothers. They and one sister showed progressive ataxia and impairment of central vision due to pigmentary macular degeneration with onset in the fourth decade. In reviewing the literature the authors point out that symmetrical calcification has been described in cases of parathyroid deficiency and has occasionally been encountered in families.

### Placebo Response.

A. A. BAKER AND J. G. THORPE (*Arch. Neurol. & Psychiat.*, July, 1957), in an article on the "Placebo Response", remind us how difficult it is to achieve valid statistical results in clinical research. The authors discuss the problems which arise in using the "double blind" technique in psychiatric investigation. Their article is based on an experimental evaluation of "Pacatal" in the treatment of incontinence. They point out several defects of this method of investigation which are usually disregarded. The active preparation may differ from the inactive one in a variety of ways over and above the presence or absence of the active ingredient, and this may affect the patient's subjective experience. Slight differences (such as different solubility or different appearance when crushed) enable the nurses to differentiate between the two, and commonly known side effects of the active drug make the difference obvious to the observer and may bias his rating. The nurses' attitude to the experimental technique and how this can affect the result is discussed, and suggestions are made on how to eliminate these defects.

### The Course of Childhood Schizophrenia.

L. EISENBERG (*Arch. Neurol. & Psychiat.*, July, 1957) gives a clear summary of the literature on a subject which has attracted much attention in recent years. In this extensive review—he quotes 97 references—he traces the historical development of the concept of childhood schizophrenia, which emphasizes the wide divergence of opinion concerning this syndrome. He feels that generalizations about childhood schizophrenia would be as unsuccessful as those on "mental deficiency" or "meningitis", and stresses the importance of specification of criteria in future reports. He states that about one-fourth of the patients can be expected to attain a moderately good social adjustment during adolescence, about one-third to deteriorate and require continuous institutional care, and the remainder to fluctuate about a marginal level. The future prospects of 50% to 75% of these children appear to be rather poor; if they cannot function under the relatively protected conditions of childhood and adolescence, it appears unlikely that they will survive the more stringent demands imposed by adulthood. He considers that there is, as yet, no evidence that any particular therapeutic agent (including electro-convulsive therapy) can be depended upon to modify the outcome of this syndrome.

### Visual Spatial Agnosia.

G. ETTLINGER, E. WARRINGTON AND O. L. ZANGWILL (*Brain*, September, 1957) studied 10 cases of visual-spatial disorder in cases of right-sided posterior cerebral lesions in right-handed persons, who had characteristic disturbance in spatial perception and manipulative skill. They conclude that disorders of visual space perception are not wholly referable to impairment of differential visual sensitivity, unilateral visual extinction, central vestibular derangement, or to a combination of these factors. Nor are they to be regarded as secondary to general intellectual impairment. A tentative explanation in terms of restriction of the field of visual attention associated with some degree of conceptual spatial loss is put forward.

### Psychological Aspects of Anorexia Nervosa.

B. C. MEYER AND L. A. WEINROTH (*Psychosom. Med.*, September-October, 1957) describe in detail a case of *anorexia nervosa*, pointing out certain features commonly found in such cases: an open conflict between the family and the patient, a preceding history of obesity and overeating which may alternate with the anorexia, associated sexual symptoms (amenorrhœa during the cachexia is universal), and admission by the patient of a desire for attention and sympathy, *plus* an attempt to divert the family notice from a supposedly more popular or younger sister. The psychodynamics are formulated along psychoanalytical lines and the postulation is made that the basic conflict is preverbal and precedipal, and this carries important diagnostic and therapeutic implications. The authors make a feature of the varying degrees of obsessive thinking and acting which are found in virtually all instances of *anorexia nervosa*, but claim that this is a façade masking an underlying psychotic process. For this reason they are pessimistic about the efficacy of superficial psychotherapy and feel that, for treatment to be successful, the therapist must be prepared to devote large quantities of time and effort, and must be able to accept frustration and failure.

### Social Factors in Attempted Suicide.

E. ROBINS, E. SCHMIDT AND P. O'NEAL (*Am. J. Psychiat.*, September, 1957) made a study of 109 patients who had been brought to a large general hospital immediately after having attempted suicide. They were examined by means of an extensive questionnaire which seemed to cover all possible facets of social and environmental stress. The diagnoses were confined to five categories: manic-depressive depression, alcoholism,

conversion reaction, socio-pathic personality and undiagnosed states. The manic-depressive patients showed significantly less socially orientated difficulties than the others. However, they had significantly better life-long adjustments, e.g. occupation, marital state, hospitalization and few arrests. They experienced feelings of depression and disgust with self and worthlessness. It is suggested that the absence of any clinically normal patient in the entire series implies that the psychiatrically well person subject to marital friction, financial insecurity, divorce or death, does not respond by attempting to commit suicide. It is remarked that no case of anxiety neurosis occurred in this series, this being the most prevalent psychiatric illness. It is concluded that simply being psychiatrically ill is not sufficient to lead to attempted suicide.

### Murder by Adolescents.

A. W. STEARNS (*Am. J. Psychiat.*, October, 1957) states that before psychiatry can seriously undertake a study of criminology it will be necessary to develop some sort of classification. A start may be made by studying a series of cases with the suggestion that they represent a clinical syndrome comparable to some of those syndromes in medicine. Four cases of murder are described in which the perpetrators have all been adolescent males. Their reputations had all been uniformly good, the victims have all been females, two scantily clad, and the crimes have been wanton and ferocious. It has been assumed that there has been gross mental disease to account for such crimes. It has been further assumed that these persons should be confined for life because it would be dangerous ever to release them. In the four murderers studied no mental disease developed. One was observed for 10 years and another for 13 years. A fifth case was studied in which the victim recovered from a vicious attack. The perpetrator received a reformatory sentence and was subsequently released on parole and has shown no evidence of conduct disorder since.

### "Marsilid."

F. AYD (*Am. J. Psychiat.*, November, 1957) reports that "Marsilid" (iproniazid) has recently been heralded in both the medical and the popular Press as a new "psychic energizer", which eliminates mood, stimulates appetite, increases weight, and restores vitality. It has been recommended for the treatment of non-psychotic depression. It was administered to 14 men and 36 women (aged 22 to 70 years) classified as psychoneurotics with the following disorders: depressive reaction, asthenia, manic-depressive reaction, involutional depression, and schizophrenic reaction. The essential complaints were weakness, lack of energy, fatigability, loss of interest, dejection, insomnia, anorexia, and loss of weight. The usual dose was 50 milligrammes two or three times per day. The patients received the drug for more than three months. There were some side effects that necessitated discontinuing the treatment. Of the 39 who continued the drug for three months, five obtained almost complete symptomatic remission, 19 were partly improved, 15 were unimproved. If these 15 are combined with 11 who had to cease taking the drug because of side effects, then it can be said that over half of the original patients that started treatment with "Marsilid" did not benefit from the drug. Although the drug is potentially useful, it should be prescribed cautiously.

## PHYSICAL MEDICINE AND REHABILITATION.

### Communication Problems in Medicine.

H. LILLYWHITE (*Arch. Phys. Med.*, November, 1957) discusses the importance of teamwork and the factors which spoil it. His paper is based on experiences at three different kinds of medical rehabilitation teams at the University of Oregon Medical School, Crippled Children's Division. He lists the following causes of miscommunication within the team: (i) Specialists sometimes show irritation at the interruption of established patterns and schedules of individual diagnosis and treatment, which often are radically altered by other specialists entering the picture. (ii) Some specialists are suspicious of others and of their methods. (iii) Specialists find it difficult to take sufficient time to discuss problems fully with other specialists. (iv) Professional class distinction plays a distinct part in preventing free interchange of information, informality and friendliness in clinics. (v) At clinic staff meetings, examining doctors often give mental diagnoses, speech diagnoses and social history, even though psychologists, speech pathologists and social consultants are waiting to report their findings. (vi) Medical specialists often tend to cluster together at clinic staff meetings and talk exclusively to each other. (vii) At clinic staff meetings there is sometimes a tendency to substitute opinion for the reporting of observed facts. (viii) Non-medical specialists often have a faulty concept of medical specialists, and are timid and suspicious. (ix) Inadequate leadership of staff meetings sometimes hampers integration and adequate discussion. (x) Final dispositions and recommendations are often not clear to the entire group. (xi) At clinics there is sometimes a tendency to talk in over-technical language. (xii) Some members are inarticulate, others over-talkative. (xiii) A noticeable inability to talk with parents and be understood is sometimes present. (xiv) An obvious inability to listen is noticeable in many specialists. (xv) Many highly specialized persons have a poor concept of people as individuals and a relative insensitivity to social situations and relationships. (xvi) An almost complete lack of understanding of the nature, functions and dangers of language is often found. The author discusses the advantages of the team approach, and presents a number of suggestions as to how the causes of miscommunication may be eliminated.

### Pneumatic Pulsatile Mobilization.

J. F. BOSMA (*Arch. Phys. Med.*, November, 1957) has studied imposed variations of air pressure within the cavities of the mouth, pharynx and larynx, with the object of discovering a possible application of this form of therapy to clinical problems of motor rehabilitation in the area of the pharynx. The clinical material consisted of patients having residual difficulty of deglutition and speech following bulbar poliomyelitis. The local effects of alternating inflation and deflation upon the cavities and upon adjacent structures concerned with their contour and motor performance were observed by cinematographic and cine-fluorographic methods. The apparatus used is described in detail. The author states that the apparatus and procedure described in his paper have a different purpose from those of other methods employed in the solution of respiratory problems. The present object is the mobilization of the intrinsic and supporting musculature in the mouth, pharynx and larynx. The procedure also provides an airstream upon which the valvular mechanism normally involved in swallowing, respiration control and speech can be exercised. The prescription and guidance in utilization of the procedure should be an individual matter in each instance, depending upon the pattern of motor disability which the patient shows at the time. When paralysis of poliomyelitis or similar causation has already produced pathological distension or expansion and an anatomical displacement, such as inferior displacement of the palate, of the tongue-hyoid-larynx composite or of the mandible, the procedure is specifically contraindicated unless external support is provided by means of a sling or similar arrangement. In selected cases the method, properly used, appears to have produced clinical benefit. The author believes that the procedure is of therapeutic value as an adjunctive measure in a general programme of rehabilitation of the mouth-pharynx-larynx area.

### Physical Measures After Operation.

F. B. MOOR (*Arch. Phys. Med.*, December, 1957) discusses physical measures in the care of the patient after operation, basing his report on a series of 100 patients and 100 controls. The object was to investigate the prevention of post-surgical phlebothrombosis and pulmonary embolism. The work was done at the White Memorial Hospital with the cooperation of the surgical service. All the patients were comparable in relation to severity of surgical procedure, age and sex. The controls were drawn at random from the record files of the previous three years. The author concludes that prolonged bed rest has certain deleterious effects, the most dangerous of which are venous thrombosis and pulmonary embolism. Early ambulation executed according to Leithauser's technique is almost a complete preventive, but early ambulation as currently practised is not entirely effective. Immediate mobilization of the patient after operation by means of electrical stimulation of the calf muscles, followed by bed exercises and then by ambulation on the first day after operation, is less strenuous for the patient than immediate ambulation, and is effective in preventing thrombosis and embolism. There were no instances of thrombosis or embolism among the 100 patients so treated.

# Special Article.

## REHABILITATION: II. THE HEMIPLEGIC.

"FAMILIARITY breeds contempt", and the problems of the hemiplegic are so familiar and frequent that an attitude of hopelessness is frequently adopted and little has been done to restore the victims of cerebro-vascular catastrophes to usefulness.

Modern rehabilitation techniques have altered this picture so successfully in the United States of America that Dr. Howard A. Rusk states that 90% of hemiplegics can be taught ambulation, self-care and urinary and fæcal continence, and 30% can be taught to do gainful work. In Great Britain the outlook is becoming altered and results are improving. In Australia our results are very bad, and it is an urgent necessity to improve them.

The general practitioner is the first person who sees these victims; upon his detailed early care and early reference of them to rehabilitation consultants will depend our future results. This is very important in our present hospital situation, with its acute bed shortage. "Stroke" is listed as the third major cause of death in the United States of America, but its morbidity has not been estimated; the morbidity rates far exceed the mortality rates.

When one is confronted with such a patient, the first necessity is to keep him alive, the second is to prevent deformity, and the third is to commence the training of the paralysed limbs at the earliest possible moment.

Whether the patient should be removed to a hospital or not depends on the facilities available for his care at home. The simple prophylactic measures necessary to prevent deformity can be carried out anywhere and do not require skilled nursing training, if the attending doctor is willing to give detailed instructions to the attendants, and to give constant daily supervision.

The techniques may be listed as follows: (i) Evaluation. (ii) Prophylaxis: (*a*) prevention of deformity, (*b*) attention to bowel and bladder abnormalities, (c) prevention of pressure sores. (iii) Retraining: (*a*) retraining of the patient in ambulation and elevation activities, (*b*) retraining of the affected arm, (*c*) retraining in the acts of daily living, (*d*) speech training. (iv) Return to usefulness: (*a*) in acts of daily living, (*b*) in productive work.

### Evaluation.

Evaluation should include the previous medical, social and vocational history of the patient and should determine the ætiology of the cerebro-vascular catastrophe—for example: Is it arteriosclerotic in origin? Is it embolic (from mitral stenosis etc)? The prognosis varies in each instance, and all programmes for the future should be related to the ætiology of the disease and the previous personality pattern, habits and work history of the patient.

### Prophylaxis.

If the lesion is gross with complete unconsciousness, the prevention of chest complications and attention to bladder function should be the first consideration. The former may be achieved by careful bed positioning of the patient and an organized programme of chemotherapy. If swallowing is deficient, a fluid balance must be maintained either by the rectal route or intravenously. The affected limbs should be placed in the best position of function to avoid deformity, and strict attention should be paid to pressure points and regular turning of the patient.

#### *Prevention of Deformity.*

In the upper limb, the common deformity to be avoided is adduction and internal rotation at the shoulder joint, and flexion of the elbow, wrist and fingers. The shoulder deformity can be avoided by placing a pillow in the axilla, and a light plaster or cardboard splint will take care of elbow, wrist and hand. All joints should be put through a range of motion at least once daily.

The lower limb tends to be flexed and abducted at the hip joint, the knee is flexed and the foot is plantar flexed and supinated. To prevent abduction, sand bags or a firm pillow should be placed on the lateral aspect of the limb in its full extent. The foot must be dorsiflexed and retained in this position by either a crêpe bandage or a light plaster splint with foot-piece. The weight of the bed clothes must be supported with a footboard or cradle. Again, the affected joints should be put through a range of passive movements daily.

#### *The Bladder and Bowels.*

The bladder readily becomes distended and over-stretched. In an unconscious patient it is better to insert a catheter and leave it if possible draining into a bottle, or to be released every six to eight hours. The risk of infection is less serious than loss of function. As function is returning, the catheter can be removed and the patient encouraged to pass urine. Careful observation of bladder dullness will prevent incontinence of urine with overflow. Until full function is restored, a catheter should be inserted once a day or even every second day to ensure that the bladder is really empty.

The bowels need not cause undue alarm as long as the abdomen is not distended.

#### *Prevention of Pressure Sores.*

To prevent pressure sores, frequent turning of the patient and attention to pressure points and smoothness of the bed are imperative. These details used to be part of ordinary nursing care, but today, when staff is scarce, the unconscious or inarticulate patient is often forgotten for the more demanding or more glamorous.

### Retraining.

When consciousness is regained and the patient is capable of understanding instructions, the retraining programme should commence. The principles are: (i) restoration of balance; (ii) training for walking and standing; (iii) training of the affected arm combined with training of the unaffected arm to take over function—for example, the left hand for feeding and writing in paralysis of the right arm; (iv) speech training.

Restoration of balance begins by explaining to the patient that his feeling of insecurity is not permanent, that the non-coordination of eye movements can be overcome, and by propping him up in bed with the upper limb supported in a sling or on a pillow to prevent drag on the affected shoulder. The length of time can be increased daily for two or three days; then with care the legs can be swung over the edge of the bed, and the patient, supported with pillows, is encouraged to swing the legs as a preliminary to being helped into a comfortable chair. The periods in a chair should be gradually increased from half an hour to two hours, alternating with a rest period on the bed. "Hasten slowly" is the motto, but the sooner the patient can be raised to the upright position, the better. If the chair is placed at the bottom of the bed within reach of the bottom rail, it can be used to assist in unaided standing and balancing exercises.

With regard to walking training, uncontrolled bed rest is just as wrong as over-enthusiastic ambulation. The patient's reaction should be watched and the length of the period in a chair steadily increased daily. In fact, in all retraining measures a small extra daily amount of activity is added to give encouragement, and great emphasis is laid on the successful performance of every new task. In an institution walking exercises are done between walking bars, but these can be improvised by placing several chairs in a row with the backs facing one another, the patient exercising between them. The function of the lower limb is easier to restore than that of the upper limb, but if the foot is difficult to control there should be no hesitation in fitting a short leg brace. Slippers should never be worn; light shoes help to maintain the position of the foot. These should be worn during rest periods on the bed. The patient should be fully dressed each morning, and when resting on the bed should have light, warm covers or none at all, to allow full movements of the limbs.

In retraining of the upper limb, external rotation of the shoulder must be restored before abduction can be achieved, so this movement must be encouraged from the earliest hours—passive abduction and then active assisted movement to prevent "frozen shoulder", which is a frequent painful and distressing complication if untreated. The good hand can be used to promote flexion and extension of the arm, forearm and hand, and to straighten out the fingers as frequently as possible. A light splint should be worn during sleep, but removed during waking hours, and movements should be encouraged.

Speech training should be begun very early; the patient's relatives should be informed that aphasia does not mean that the patient's mentality is affected. To reestablish communication at the earliest moment is an urgent necessity. All exercises should be related to the acts of daily living by

recognition of familiar objects, first with nouns and then with verbs appropriate to them—for example, "cup-drink", "knife-cut", "razor-shave", etc. Every attendant, relative and friend coming in contact with the patient should be instructed to encourage the patient with these exercises.

### Return to Usefulness.

When the basic measures in the acts of daily living are complete, return to a work situation and employment should be the aim if possible. If the early measures have been faithfully carried out, then the first stage of the battle is won; if they have been neglected, weeks and months will be needed to regain the lost ground. Skilled retraining by a qualified team is the ideal, because the techniques involved are not taught in the ordinary medical curriculum; but many helpful suggestions can be given to the general practitioner by the rehabilitation consultant, who is willing to offer advice at any time to have the techniques begun early—that is, in the first hours.

The acts of daily living include washing, toilet and bath, dressing, feeding and transport. The simpler functions can all be taught by any intelligent person who is willing to receive instructions.

The application of occupational therapy and physiotherapy techniques hastens the recovery so much that no effort should be spared to seek advice and, if possible, to send the patient to a rehabilitation centre for training. The group exercises and association with other people overcome the personality changes and give encouragement impossible elsewhere.

Attention to detail and common sense are the keynotes of these techniques, with an altered outlook towards these patients. Their condition is not hopeless, and the patient whose prognosis appears hopeless in the first weeks will make surprising progress in six months; if there is no progress after this time, the case must be reconsidered. It is a matter of national economy to keep everyone useful in an ageing community, and a challenge to the medical profession to be the leaders in this campaign.

### Summary.

In summarizing, we must remember the following:

1. Initiate rehabilitation measures as soon as the patient is examined.

2. Observe prophylactic measures in all phases of the patient's medical care.

3. Refer the patient early for retraining, seeking the advice of the rehabilitation consultant in the early stages of planning medical treatment, to prevent undue deformity and psychological complications.

M. NAOMI WING.

Sydney.

# British Medical Association.

## VICTORIAN BRANCH: SCIENTIFIC.

### SECTION FOR THE STUDY OF ALLERGIC DISEASES.

A MEETING of the Section for the Study of Allergic Diseases of the Victorian Branch of the British Medical Association was held on November 7, 1957, at the Medical Society Hall, 426 Albert Street, East Melbourne. The meeting took the form of a symposium on asthma.

### Symposium on Asthma.

#### *The Causes and Diagnosis of Bronchial Asthma.*

DR. P. WARD FARMER discussed the causes and diagnosis of bronchial asthma. He said that bronchial asthma could be defined as an atopic illness characterized by recurrent or periodic attacks of dyspnœa, most marked in the expiratory phase, while *status asthmaticus* was a severe and continuous state of bronchial asthma which was not relieved by ordinary therapeutic agents. The diffuse bronchiolar obstruction was characterized by a high degree of reversibility, while obstructive pulmonary disease which was not reversible was usually classed as emphysema. Asthma and emphysema had similarities, and clinically they overlapped to such an extent that it might be impossible to separate them in long-standing cases, while emphysema was the most common and important complication of asthma. The bronchial tree was a vital life line, designed to minimize turbulence and the effects of gaseous viscosity and to spare muscular effort in the act of ventilation. Turbulence was undoubtedly a striking accompaniment of asthma, and accounted for the characteristic wheezes. Asthma was accompanied by a reduction in the vital capacity, and the residual volume was increased at the expense of the vital capacity. In asthmatics there was a reduction in the speed of air flow especially during the expiratory phase. The patency of the airway might be affected by contraction of bronchiolar smooth muscle, or by encroachment arising from swelling and thickening of the walls through œdema or from inflammatory exudate.

Dr. Farmer went on to say that although there was no direct evidence in man that bronchospasm was the cause or principal factor in the development of the asthmatic attack, there was a certain amount of indirect evidence. When patients with bronchial asthma were given 0·02 to 0·06 milligramme of histamine by intravenous injection, they almost invariably suffered an abrupt reduction in vital capacity and a slowing of the expiratory rate, but in non-asthmatics no alteration was noticed with that dose. Acetylcholine would likewise induce attacks in asthmatics, but sympathomimetic drugs and aminophylline would prevent or relieve those induced attacks. Inhalations of an aerosolized extract of the appropriate allergen would be followed by asthma after an interval of several minutes, but that was less easily relieved by bronchodilators than were the attacks induced by histamine and acetylcholine. Bronchoscopists were well aware of the spasm induced by the tip of the bronchoscope, and the presence of a foreign body might likewise give rise to segmental spasms of the bronchi. It was not unlikely that in asthma the bronchial secretions themselves, having undergone marked changes, might actually play the part of a foreign body and induce bronchiolar contraction under certain conditions. The bronchial tree was lined with mucous membrane consisting of secreting as well as ciliated cells. The mucus kept the movement of the cilia going, and the system acted as a trap for dust particles and bacteria. When mucus was absent, the ciliated cells were converted to goblet cells which secreted mucin, and infected mucinous material might actually cause bronchospasm. Most would agree that bronchospasm played an important part in causing obstruction in bronchial asthma. Halpern described the findings on bronchoscopy, followed by biopsy, before, during and after attacks induced by inhalation of specific allergens. Œdema of the bronchial wall with marked increase of eosinophils occurred with great suddenness and was similar to the œdema induced in animals. In subjects dead of *status asthmaticus*, the striking lesions comprised widespread obstruction of the small bronchi and bronchioles by thick desiccated mucus, while the lining mucosa was pale and boggy and thrown into folds. There was little doubt that swelling of the bronchial walls and exudate also played an important part in the obstruction to air flow.

Discussing the causes, Dr. Farmer said that probably the precipitation of an asthmatic attack was influenced by parasympathetic over-activity with the release of histamine and acetylcholine, the latter intensifying the allergic tissue response; but the reactivity of the bronchial tree seemed to wax and wane unpredictably. A great deal was known about the precipitating causes of asthma, but they would not "trigger off" asthma in normal individuals, and many patients had severe sinus allergy due to air-borne allergens without ever having asthma. Therefore there must be some constitutional factor or "make up" which predisposed people to attacks, but it was not known what that was. When a patient was being investigated, it should be borne in mind that several factors might be involved, and a broad approach was most important. Attacks were most commonly precipitated by exposure to air-borne allergens, by infection in the respiratory tract or by focal infection, but could be "triggered" in a reflex manner by sinus disease, emotional stress and digestive upsets. Allergic, infective and other "triggers" might combine together or successively to produce an individual attack.

Dr. Farmer went on to say that air-borne allergens in the inspired air were the most important precipitating cause of asthma. They were minute, particulate, buoyant forms which entered by penetration of the upper or lower parts of the respiratory tract and might produce almost immediate symptoms of nasal irritation, cough and dyspnœa, although there might be a latent period between exposure and the onset of symptoms. Seasonal asthma occurring in the spring was caused by grass pollens in nearly every case, but pollens from the Compositæ such as capeweed, dahlia or plantain could cause attacks. Perennial asthma was most often caused by dry particulate matter of vegetable or animal origin, so altered that it could rise and

be carried in the atmosphere. "House dust" allergen was the most important in that group, but in spite of intensive research the allergenic substances had not been identified. Other important air-borne allergens were those of animal epithelia, especially cat hair, feathers and horse dander, while other potent inhalants were kapok, linseed meal and castor-oil bean. Probably 60% of all asthmatic attacks were precipitated by either "house dust" or grass pollens. Air-borne allergens could cause attacks at any age, and in many cases of pollen asthma the first attacks developed after the age of 50 years. Inhalation of foods such as wheat flour could precipitate attacks in sensitive subjects.

Asthma caused by the ingestion of foods was chiefly a problem of the first two decades of life, and food allergy tended to disappear when adult life was reached. Children might suffer severe attacks brought on by ingestion of such foods as cereals, nuts, milk, egg white or fish. However, Dr. Farmer said that in his opinion foodstuffs rarely caused asthma in adults, although it was true that occasionally a sensitivity was retained all through life—for example, to egg white. Irritating indigestible foods might caused attacks in both children and adults.

Drugs and therapeutic agents might cause asthma by inhalation, but more often by injection or ingestion. Perhaps the best known examples were aspirin and penicillin and to a lesser extent sulphonamides. Many were non-protein and acted by linkage to a body protein to form complete antigen. However, biological products and sera might also induce asthma in sensitive cases.

Non-specific factors might become more important than specific air-borne allergens in certain cases. Amongst them might be mentioned traffic fumes, industrial smoke, tobacco smoke, therapeutic smoke (asthma cigarettes), the over-use of therapeutic sprays, and insecticides, while sulphur dioxide and halogens were especially harmful. Nervous factors such as panic, anxiety and anger might help to "trigger" an attack.

The weather as a cause of attacks deserved special mention, but the asthmatic was highly individual in that regard. A drop in barometric pressure and excessive himidity were injurious to asthmatics, and the explanation might lie in the fact that there was less evaporation from the skin, leading to a higher respiratory rate and lowering of the carbon dioxide level in the blood. Winds might carry pollen hundreds of miles, and in Melbourne a north wind was particularly noxious to pollen-sensitive patients. Cold south winds also aggravated symptoms in many cases. However, the role of climatic factors remained obscure, and little could be said specifically; Hyde Salter's dictum that "the patient should live in the opposite climate to that in which he seems worse" still stood.

Dr. Farmer then referred to infection and asthma. He said that there was no doubt that either acute or chronic infection would cause asthma in an individual with a susceptible background. Acute infection could cause asthma at any age, and often appeared to be the sole cause of attacks in young children up to the age of three or four years; but as those children grew older they acquired sensitization to inhalant allergens such as "house dust" and grass pollens, and then either infection or inhalants and to a lesser extent food allergens might be the cause. Predisposing causes to infection leading to asthma in children were the specific infective diseases, particularly whooping-cough, measles, pneumonia and influenza, and acute infections of the upper part of the respiratory tract. Inhalant allergens such as "house dust" might predispose the mucous membrane to infection. Chronic infection in the lymphoid tissue of the tonsils and pharynx and in the nasal accessory sinuses could cause asthma, while oral sepsis in the form of root abscesses might also be a cause. When the onset was in middle life or later, a chronic infective focus, which might have existed in the upper part of the respiratory tract some years prior to the onset of asthma, was often the cause; those subjects tended to have hyperplastic sinus disease and no family or personal history of allergy, and skin tests usually gave negative results. The specific causes of infective asthma were bacteria and their products, and the common organisms involved were streptococci, staphylococci and diplococci. At Prince Henry's Hospital it had been found that in acute asthmatic episodes culture of the sputum produced a profuse growth of *Hæmophilus influenzæ* in many cases, while pneumococci in abundance had been grown on culture in a smaller number of cases. Whether viruses played a primary or secondary role was uncertain, but probably the secondary bacterial invaders were more important. The results of treatment with antibiotics and sulphonamides were unreliable in many cases, and when chronic infection was established they produced little benefit. It was noticed that most asthmatic attacks in childhood were accompanied by a raised temperature, but Dr. Farmer said that in his opinion that did not necessarily indicate that the cause was an infection. The sputum in attacks might be misleading. Mucopurulent sputum was not diagnostic of infection by bacteria or virus, often contained predominantly eosinophils with no pathogens, and in practice was resistant to antibacterial measures. Thick, greenish, purulent sputum with small yellow plugs usually contained pathogenic organisms and neutrophils. Löffler's syndrome of transient pulmonary consolidation, fever and high eosinophilia occurring in young asthmatics was probably of an infective nature, but some cases might be examples of extreme mucoid impaction of bronchi in asthmatics. Patients with genetic agammaglobulinæmia had an enhanced susceptibility to bacterial infection characterized by repeated attacks of sinusitis, septicæmia and pulmonary infections, and it was possible that some cases of infective sinusitis associated with asthma might belong to that group; but so far as Dr. Farmer knew, no special study on the relationship of asthma to that deficiency had been carried out.

Dr. Farmer then discussed the question of investigation. He said that the history was most important, as it frequently gave a guide to the type of asthma from which the patient was suffering. Careful and comprehensive questioning about mode of onset, season, environment and diet in relation to attacks should be carried out. Hay-fever symptoms would suggest an allergic basis for attacks; but symptoms of allergic rhinitis might be called "nose colds" by the patient. A history of infective sinusitis, nasal polyposis or repeated tonsillitis would suggest an infective cause. Inquiry about particular dusts irritating the mucous membranes should be made, and also about whether antibacterial drugs relieved the attacks. The patient was asked about the nature and quantity of sputum, and whether it was present every day. Emotional factors and family relations were most important. The family history usually revealed allergic disease in relatives, but not always. Lastly, any past illness, especially previous allergic episodes, and specific acute infections should be noted. A thorough physical examination should follow a detailed history. During an attack wheezing and dyspnœa were obvious, and auscultation revealed prolonged expiration with inspiratory and expiratory rhonchi, but an injection of adrenaline should abolish or greatly lessen the signs. Between attacks there might be no abnormal signs or symptoms, but expiratory rhonchi were often heard when the patient breathed deeply through the open mouth. Other investigations included an X-ray examination of the sinuses and chest, a specialist's examination of the nose and throat, examination and culture of the sputum for bacteria and fungi, and a blood examination for leucocytosis and eosinophilia. A test meal examination might reveal achlorhydria. Skin tests for allergy were as important as the history; sometimes the latter might give misleading information, as the patient would blame an inhalant allergen for attacks, but skin testing did not reveal sensitivity to that allergen. Skin tests with foods were less reliable than those made with inhalants, and elimination diets might give more useful information. Scratch tests should always be carried out before intradermal tests, so that the degree of the patient's sensitivity could be assessed before any potent allergen was injected; dangerous reactions had resulted from injecting a potent extract into very sensitive patients. Another important rule was not to carry out more than five or six intradermal tests on one day. With both scratch and intradermal tests much depended on good technique, potent extracts and frequent control tests with buffered saline, the last-mentioned applying particularly to patients with sensitive skins, such as the eczema-asthma child and adults with mild dermographism. A control solution contaminated by allergen extract might cause error in testing. With marked dermographism it might be impossible to obtain a reliable reading of results, and the tests should be repeated at a later date. A majority of patients reacted to a limited range of inhalants, the most common being cat hair, feathers, "house dust" and grass pollens; but large reactions might be given to horse dander (especially in the eczema-asthma child), kapok, cattle hair and linseed meal. Antihistamines taken orally might reduce the size of the weal. All patients should be retested once or twice to make sure that they showed the same pattern of sensitivity, and results should be carefully correlated with the history. It had to be stressed that positive reactions might have no significance in some cases; for example, when attacks occurred only in the winter and large reactions were given to grass pollens, the latter could not be implicated.

Discussing the differential diagnosis, Dr. Farmer said that that should not be difficult when a well-taken history was

combined with a thorough physical examination. However, in early childhood attacks were often labelled "bronchitis" or pneumonia; in those an expiratory wheeze was often heard at the end of the illness. Other diseases in childhood which might cause confusion were congenital laryngeal stridor, other obstructions of the upper air passages, a foreign body in a bronchus, laryngo-tracheo-bronchitis, bronchopneumonia, whooping-cough, neoplasms and cysts. In adults, mild cases were often diagnosed as "chronic bronchitis". Bronchospasm might be associated with pulmonary tuberculosis or bronchial carcinoma. A retrosternal goitre might cause confusion in some cases, while a foreign body in a bronchus might induce symptoms of asthma in an asthmatic patient. Idiopathic emphysema might be mistaken for asthma. Perhaps most confusion arose with "cardiac" and "renal" asthma. The paroxysmal nocturnal dyspnœa associated with cardiac failure and uræmia was not relieved by an injection of adrenaline, but was usually relieved by an injection of morphine. Such patients had cardiac enlargement, hypertension and other signs of cardiac or renal disease. However, it was not uncommon to see patients with organic heart disease, especially rheumatic valvular disease, suffering from bronchial asthma. The differentiation of cardiac asthma from bronchial asthma was most important, as the dyspnœa from the latter was usually compatible with a fairly long and useful life, whereas when dyspnœa resulted from cardiac failure and was paroxysmal in type, the outlook was very grave. When chronic infection of the bronchial tree was established in long-standing asthma, gross emphysema and chronic bronchitis usually resulted, often with the eventual development of *cor pulmonale* and pulmonary hypertension.

Dr. Farmer said, in conclusion, that every case of asthma should be regarded as highly individual, and failure to examine all the facts and adherence to one point of view would result in errors in ætiological diagnosis. In most cases several precipitating causes were involved. In his opinion too much stress was laid on the emotional factor, although it had to be admitted that tension appeared to be the main cause in a small number of cases. As allergists they should critically review their theories of causation from time to time, and try to encourage more biochemical and clinical research into that elusive disease.

*The Upper Part of the Respiratory Tract in Asthma.*

DR. R. H. O. DONALD discussed the fate of the upper part of the respiratory tract. He said that asthma knew no boundaries and spared no race or age group; it might occur from infancy to old age, in all races and in all parts of the world. It was usually acute and intermittent at first, but if untreated frequently became chronic. Most patients who suffered from asthma had pathological changes in both the upper and the lower sections of the respiratory tract. Consideration of the upper part of the respiratory tract in asthma was sometimes overlooked, as some clinicians and pathologists studying asthma tended to concentrate on the condition of the lower part of the respiratory tract, and gave scant attention to the upper part. He found it best to study the involvement of the upper part of the respiratory tract in asthma under three headings: (i) cases whose origin was purely allergic; the condition might be either seasonal or perennial, or perennial with added seasonal incidence; (ii) cases which were allergic, but which were complicated by superadded infection; (iii) cases which were purely infective. Naturally the groups merged into one another; thus the classification was not hard and fast. Considering the first or purely allergic group, Dr. Donald said that the majority of such patients were sensitive to seasonal allergens such as grass pollens, so their attacks of nasal disturbances and asthma occurred seasonally, particularly in the spring and summer. Other patients with perennial nasal symptoms and asthma may have attacks of allergic rhinitis or asthma at any time, and such people were frequently found to be sensitive to such allergens as house dust, kapok, animal hairs and danders, fungi and, very occasionally, to foods. Any of those patients might develop an infection in their respiratory tract, which might be in the nose, sinuses or lungs; that introduced the second group of asthmatic sufferers—patients who had superimposed respiratory infection on either their seasonal or their perennial allergies. All patients with allergies should be seen and treated as soon as possible, and that was particularly true of the second group, for if patients with mixed allergy and infection were left untreated for long they became particularly resistant to therapy. Dr. Donald said that he found it best to control the allergy first and then to treat the infection, or to treat both allergy and infection simultaneously. The third group—patients who developed nasal symptoms and asthma from purely infective causes—might have the upper part of the respiratory tract intimately involved. The attack of asthma in those patients particularly followed infective rhinitis and sinusitis, or the asthma might be precipitated by infective involvement of all the nasal sinuses; in other words, basic pansinusitis might be present. Dr. Donald said that he wished there to make the point that in investigating and treating those asthmatics, the condition of the whole of the respiratory tract had to be considered; but for the purposes of the discussion he would confine himself chiefly to the upper part of the respiratory tract.

Dr. Donald went on to say that any asthmatic patients who had involvement of the upper part of the respiratory tract were found to have a long history of nasal disorder and catarrh for years. They frequently had a nasal and post-nasal discharge, and in some cases nasal polypi were present. What did one find on examination of the nose in patients who suffered from asthma and who had infection in the upper part of their respiratory tract? The nasal mucous membrane was found to be pale and œdematous, the turbinates were enlarged and pitting, and secretions were usually present and might be purulent. Examination of nasal smears and sections of the mucous membrane would often reveal eosinophilia. If the condition persisted for long, and the infection got a strong hold in the sinuses, the appearance of the nasal mucous membrane might alter, and instead of having the pallor characteristic of the allergic nose, the nasal mucous membrane might be red and inflamed from the progressive infection. In patients who had a basic allergy, the nasal and accessory nasal sinus linings became swollen, as contact with offending allergens caused an increased capillary permeability in those linings. The swelling of the mucous membrane would prevent drainage from the sinuses through the ostia, and so a natural incubating chamber was produced which allowed the invading organisms to multiply. That condition predisposed the patient to secondary bacterial infection and the occurrence of chronic infective sinusitis. The discharge from those noses was purulent, and contained many pus cells, organisms and eosinophils.

Dr. Donald then said that all patients with asthma should be investigated thoroughly in routine fashion. First, an accurate and careful history should be taken and a search made for any offending allergens. Next, a full range of relevant skin tests and later selected intradermal tests should be carried out. When necessary, food elimination diets could be used. If the presence of infection was suspected, as was frequently the case, X-ray examination of the sinuses might be helpful diagnostically, and should be carried out as a routine procedure. The sinuses were frequently found to be clouded, particularly in the maxillary and ethmoidal areas. Nasal smears should be prepared and stained, a proof puncture performed, and the washings returned through a second sterile cannula and then examined culturally for organisms. The appropriate anti-allergic and anti-infective treatment should then be instituted according to the results of those investigations.

Dr. Donald said that pansinusitis or hyperplastic rhinitis with polyposis might occur in the upper part of the respiratory tract of patients whose asthma was complicated by or due to infection. On examining the nose of such patients, one found soggy, pale grey, swollen mucous membrane, enlarged and œdematous turbinates and polypi of varying size. The mucous membrane might have a reddened appearance in some cases. Those patients should all undergo routine allergic and infective investigation. If any positive result from the skin tests linked up with the positive findings from the history of such patients, a course of desensitizing injections with the appropriate allergenic extract should help them. That desensitization should be accompanied by removal of the polypi and later by treatment of the upper respiratory infection present. Many of the patients with that type of allergy did not give positive results to skin tests to ordinary allergens; some of them had developed an allergy to their own organisms or to the products of those organisms—in other words, they had a pure intrinsic allergy. Those patients were most difficult to treat. In some cases he had obtained good results by carrying out antral washings and culturally examining the fluid returned; this would often reveal the infective organism. Sensitivity tests were carried out *in vitro* against the organism implicated, and the appropriate antibiotic was determined. Dr. Donald said that he then administered the antibiotic to the patient, often with beneficial results, affecting the asthmatic attacks and also the upper respiratory infection, both of which decreased in severity and frequency. He found it best to accompany that therapy with a series of antral washouts. The Proetz method of postural nasal drainage, using good isotonic vasoconstrictor nasal drops, would give considerable help to those

patients, as it helped them to maintain their airway, and it also helped to drain the accessory nasal sinuses by shrinking the swollen mucous membrane round the ostia and so rendering the ostia patent. That treatment had to be carried out regularly and faithfully by the patient several times a day.

Dr. Donald further said that in his opinion there was a place for nasal surgery in the treatment of certain selected allergic patients suffering from asthma. Those who were helped most by such surgery were patients who had gross infection in their sinuses, particularly in the maxillary, ethmoid and sphenoidal sinuses, and also patients who had an obstructed airway. In the main it was best to avoid major nasal surgery in hypersensitive patients. Such surgery should particularly be avoided in subjects with the Francis triad—chronic asthma, nasal polyposis and aspirin sensitivity. When surgery was indicated for those allergic patients, either to help clear sinus infection and promote adequate drainage from the sinuses, or to help in the establishment of a good airway, it should always be the aim of the surgeon to disturb the mucous membrane lining of nose and sinuses as little as was reasonably possible. The physiological reason for that was to leave the cilia undisturbed so that they could carry out their normal activity. The cilial lining of the upper part of the respiratory tract was its first line of defence. The cilia were tiny hair-like structures on the mucous membrane, covered by a thin layer of mucus. They beat perpetually, always beating in a constant direction—in the nose posteriorly towards the naso-pharynx, in the lungs upwards towards the pharynx, and in the sinuses towards the ostia—so as to carry toward the openings any foreign bodies which became caught up in their mucous stream. The mucous stream was propelled along by the beating cilia, and if there was any interference with that flow the patient was at a disadvantage trying to eliminate pus, debris and dead bacteria from nose and sinuses. Any surgery undertaken on nose or sinuses must be carried out with due care to interfere as little as possible with cilial action; therefore the surgeon working in that area should reduce scarring to a minimum. The surgery which would help carefully selected asthmatic patients was sometimes submucous resection of deviated septa or septal spurs to allow a better airway and more efficient drainage from infected ethmoid cells. It was doubtful whether the removal of portions of turbinates or cauterization of turbinates when they were enlarged was of much value, as those operations caused excess scarring of the ciliated mucous membrane. The use of a bipolar electrode, on the other hand, might help to reduce the swelling of enlarged turbinates, and caused minimal scarring. In selected asthmatic patients who had gross suppurative pansinusitis and hyperplastic rhinitis, and who would not respond to exhaustive anti-allergic and anti-infective treatment, planned major operative surgery on the sinuses might give considerable relief. Such patients must be carefully selected, and due regard must be paid to all the considerations mentioned before operation was decided upon. On no account should such radical surgery be undertaken on aspirin-sensitive patients.

Dr. Donald said that some authorities in America—namely, Van Alyea and Shambaugh—held that in operations on the accessory nasal sinuses of asthmatic patients, the mucous membrane lining those sinuses should be left in position, no matter how infected it was. That view was held because those authorities considered that the regenerative powers of the mucous membrane were so great that, once adequate drainage was given to diseased sinuses, the mucous membrane lining those sinuses would regenerate and return to normal. Other well-known authorities—namely, Cooke and Grove—maintained that when radical sinus surgery was performed on the accessory nasal sinuses, adequate drainage should be given, and also the mucous membrane lining the affected sinuses should be thoroughly stripped and removed completely, even in asthmatic subjects. Dr. Donald said that in his opinion the optimum treatment lay between those two views. First, adequate drainage of all accessory nasal sinuses should be established; then attention should be given to the mucous membrane. When that was grossly diseased, it should be removed, but all reasonably healthy tissue should be left undisturbed *in situ*. His reason for that statement was that asthmatic patients responded very badly to having the mucous membrane of their sinuses disturbed, especially those who were very sensitive to allergens—in other words, those who suffered from extrinsic allergy. Therefore it was wise to traumatize the nasal linings in those patients as little as possible after removing any grossly diseased areas. Dr. Donald stressed again that drainage of all infected sinuses—maxillary, ethmoidal, frontal and sphenoidal—must be adequate, and every effort made to clear up the nasal and sinus infection. Dr. Donald finally reminded those present that only a very small percentage of asthmatic patients should ever come to radical sinus surgery, as the great majority of asthmatic patients would respond to conservative, properly planned anti-allergic and anti-infective treatment.

### *The Treatment of Asthma.*

Dr. V. G. Bristow discussed the treatment of asthma. He said that the immediate relief of a state of asthma was usually based on three common drugs—adrenaline given by subcutaneous injection, ephedrine hydrochloride or ephedrine sulphate given by subcutaneous injection or aminophyllin given by intravenous injection. Before adrenaline tartrate (1/1000 solution in doses of five to fifteen minims) was used, the clinician should inquire whether it had been used before. If not, a test dose of one to three minims should be given to see whether idiosyncrasy was present; therapeutic doses in such circumstances could produce fatal collapse. If there was no contraindication, at least 10 minims should be given subcutaneously. The minim-a-minute technique was not very useful, as vasoconstriction in the area prevented absorption. In emergency, a trick was to give up to 15 minims in five or six well separated doses. In most cases an initial dose of 10 minims or so was greatly reinforced by a further injection of five minims or so about 15 minutes later. The intravenous administration of adrenaline, even in 1/10,000 solution, was considered too dangerous to be used. Death could be caused by ventricular fibrillation. Ephedrine hydrochloride, three-quarters of a grain, was given subcutaneously or intravenously. Subcutaneous injection was too slow for practical use, while intravenous injection had unpleasant although harmless reactions. The addition of hyalase to a subcutaneous injection caused more rapid absorption, and was almost as effective as intravenous injection. Ephedrine should not be used if the patient had taken much adrenaline. The ephedrine induced a severe state of shock in such patients, and sooner or later would cause sudden death. Aminophyllin would often relieve severe spasm when given intravenously in a dose of 0·25 or 0·5 gramme in 10 or 20 cubic centimetres respectively, even when the patient was "adrenaline-fast". However, again, severe shock could follow intravenous injection, and a few deaths had been reported. The use of intramuscular injection was often surprisingly effective, but generally the response was more outweighed by severe pain. Aminophyllin suppositories were often useful, particularly for children, but aminophyllin tablets had little use in *status asthmaticus*.

Dr. Bristow went on to say that oral cortisone administration was too slow for acute attacks, taking one to five days to produce relief. ACTH in doses of 10 to 40 milligrammes given by the intravenous drip method could produce relief in six hours or so; but all those preparations had recently been superseded by "Solu-Cortef", a soluble salt of hydrocortisone. It was given in a dose of 100 milligrammes by direct intravenous injection, two minutes being taken to give the injection in two cubic centimetres of solvent. That treatment produced startling relief in about 20 minutes, and although limited by all the usual contraindications of the steroids, it could revolutionize the casualty treatment of *status asthmaticus*. Subsequent oral maintenance therapy with cortisone was, of course, necessary while the causes of the current *status asthmaticus* were dealt with.

Dr. Bristow then discussed symptomatic self-treatment by the patient by oral therapy. He said that in general terms he thought that the patient should never own a hypodermic syringe. He had seen two patients who died while using a syringe, but he had never seen a patient die with oral therapy. Preparations of isoprenaline were convenient and safe as tablets for use under the tongue. Such preparations were not very potent, but had a place in treatment in mild cases. Most other preparations contained ephedrine. That was fairly efficient, but was slow acting, and the side-effects could be distressing. Most preparations contained a barbiturate or chloral hydrate to counteract those effects. It was difficult to adjust the ratio of ephedrine and sedative to suit the various responses of the patients. A new synthetic ephedrine-like drug, "Orthoxine", was now available. It was moderately efficient and had few side-effects, but it was very expensive. Aminophyllin was present in many mixtures and tablets in association with ephedrine, but alone was rarely of much use. Elderly asthmatics, with perhaps some congestive cardiac failure, were often relieved by continuous use of aminophyllin tablets. Aminophyllin suppositories were of some help in giving the patient a night's sleep, but they were not a convenient preparation.

For the patient who was resistant to all other forms of treatment, temporary maintenance with steroids, usually a

cortisone preparation for oral use, was indicated. (Dr. Bristow said that he was assuming the absence of contra-indications.) The steroids should be used only in treating self-limited conditions or for controlling symptoms while logical treatment was organized and applied. Maintenance of a chronic asthmatic without a continual attempt at logical treatment was to be avoided as strongly as symptomatic treatment with an adrenaline spray.

Dr. Bristow further said that logical or long-term treatment consisted of identifying the allergens concerned and instructing the patient to avoid them. That might be easy with a few food allergens, but was obviously impracticable in most cases. The next approach was to use subthreshold doses of the allergens to build up the patient's resistance to them. That desensitization frequently failed if ancillary causes of the patient's asthma were neglected. The most important ancillary condition was infection, usually respiratory. Acute infection was treated by the relevant antibiotic and drainage. Chronic infection was, of course, harder to treat, but even that could often be treated satisfactorily. Nasal polypi should be removed by an efficient but conservative surgeon. Other pathological conditions, such as thread-worms in children, should be eliminated before logical treatment was undertaken. The emotional situation of the patient must be understood and, if possible, resolved. Intercurrent infection must be eliminated as much as possible, and vitamin *A* concentrates were very useful there. Maintenance therapy with an iodide mixture should always be tried, as it often helped the patient. Great care must be taken during desensitization that the condition of the patient was not made worse. Overdosage was readily indicated with an immediate reaction. Dust and pollen extracts might produce an immediate reaction, but bacterial vaccines were difficult to control, as the ill effects were not closely related in time to the injection. Desensitization to foods was of doubtful value and was rarely undertaken. Other logical measures were physiotherapy to teach adequate use of the diaphragm, to relax skeletal muscles and so avoid panic, control of the emotional situation if possible, and, as a last resort, a change in the meteorological or geographical environment if indicated.

## Discussion.

DR. DESMOND A. PRENTICE, in opening the discussion, said that asthma was without doubt the most important clinical condition met with in the field of allergic disease. The fact was accepted that by definition asthma was a syndrome, and like the other common syndromes—for example, congestive cardiac failure or jaundice—could be considered for the purpose of clinical discussion under various headings, such as ætiology, diagnosis, prognosis, treatment, etc. Since those features had already been covered in detail by the preceding speakers, it would be redundant to speak of them further. What he proposed to consider was that fundamental discovery of sensitization phenomena and its application to that group of clinical conditions that were now known as the sensitization or allergic diseases, particularly in reference to asthma. At that stage the question might be raised why that discovery of sensitization was such a fundamental one. It could be answered in definite terms in the following way. (i) For the first time a clear-cut, basic ætiology on scientific grounds could be given for the group of diseases in question. (ii) A logical method of precise identification by immunological testing of the causal sensitizing allergens was now available. (iii) A new and specific method of treatment by desensitization could be utilized, based on the anti-anaphylactic methods of Rosenau and Anderson. Those three facts—the immunological mechanisms involved, precise identification by testing and specific treatment by desensitization—opened an entirely new vista for the allergic diseases. Today they still held pride of place and formed the foundation on which the consideration of asthma and allied conditions must be based.

Dr. Prentice said that in any branch of science, the historical development of knowledge gave a clearer understanding of present concepts. That fact, indeed, well applied to the discovery and formulations of sensitization and its relationship to asthma and allied diseases. He proposed to trace its evolution briefly. From the middle of the nineteenth century, a new science of bacteriology was developed. That, as a scientific study, dated from the researches of Pasteur, followed by those of Koch and an outstanding scientific group of investigators. They had initially been concerned with the identification of various microorganisms as the causal factors in infective disease of animals and man, such as cholera, anthrax, tetanus, rabies, tuberculosis, dysentery and a host of others. That earlier phase was concerned with the more general morphological characteristics of bacterial organisms, and the scientific study of infective disease had become the province of the bacteriologist. That work led logically to the next phase, which was to investigate the relationship between infection and resistance of the host, both natural and acquired—in other words, immunity problems. Even there it was to be noted that Pasteur had already used attenuated cultures as vaccines in rabies and cholera. However, in general the development of knowledge on scientific grounds concerning the various immunity reactions which could occur when serum was mixed *in vivo* and *in vitro* with various bacteria, their products, foreign proteins or foreign cells, dated from 1888, when Nuttall showed that defibrinated blood could be bactericidal. Buchner, in 1889, showed that that was due to a property of cell-free serum and was lost by heating. By the turn of the century, production of specific antitoxins, bacteriolysis, agglutination phenomena, complement and opsonins had been discovered. In 1898 Ehrlich formulated his classic side-chain theory on the mechanism of serum reactions, which had played a prominent part in immunological studies. That phase, therefore, had led to the development of a new branch of science, really as an offshoot of bacteriology—namely, immunology. Pertinent to the discussion was the discovery in 1890, by von Behring and Kitasato, of the antisera to diphtheria and tetanus toxins, and the extensive use of the former in immunization. After its injection a peculiar group of reactions was found to occur in some cases, characterized by what could today be termed weal and flare phenomena—namely, generalized pruritus and erythema, urticaria, angioneurotic œdema, asthma, rhinitis, serum sickness and death. Similar types of reaction had been experimentally observed before by Magendie, Flexner, Ehrlich, Theobold Smith and others, following repeat serum injections into rabbits—in fact, Ehrlich had termed them the Theobold-Smith phenomena—but none had attempted to explain them on precise scientific grounds until Ricket in 1902, after a series of investigations spread over several years, formulataed the basic concepts of that phenomenon and applied to them the term anaphylaxis. His basic tenets were still correct, although the mechanism he postulated was not. Over the next few years that phenomenon was fully investigated, and its sensitization mechanism of antigen-antibody reactions, specificity, anti-anaphylactic procedures etc. was elucidated by several investigators, especially Rosenau and Anderson in 1906. The position, therefore, at that stage could be summarized in the following way. In the first phase there was formulated the new science of bacteriology, in the second phase the science of immunology was developed as an offshoot to bacteriology, and there as an incidental clinical finding came the discovery of anaphylaxis, which was the first classical sensitization reaction noted and studied. On that anaphylactic phenomenon the third phase followed, namely, the tie-up with what eventually came to be termed the allergic diseases. That, in retrospect, was the next logical step, for the observed reactions which were seen in anaphylaxis and many ætiological factors unexplained until then were identical. In addition, it had been known for many years that contact with certain substances, such as pollens, foods and even physical factors, could produce rhinitis, asthma and urticaria; the reason why, of course, was not known. Weichardt, in 1905, and Wolff Eisner, in 1906, had suggested that hay fever was an anaphylactic phenomenon. Vaughan, in 1907, had shown that many protein fractions in foods, pollens and bacteria were the factors that could induce anaphylactic sensitization. Auer and Lewis, in 1910, noted that the important finding in anaphylactic shock in guinea-pigs was an intense bronchospasm, and that led Meltzer in 1910 to suggest that the asthmatic syndrome in man was also an anaphylactic phenomenon. In 1911, Noon and Freeman had proved the allergic ætiology of seasonal hay fever or asthma; they introduced a standardized scratch and conjunctival test procedure, followed by the pre-seasonal method of specific desensitization by hypodermic injection of gradually increasing amounts of extract. It was also in that year that Cooke introduced the intracutaneous test for general allergic diagnosis. In passing, it had to be mentioned that Pirquet, in 1906, had first used the term "allergy" as a descriptive term meaning altered activity, reactivity or energy of tissues, since he took exception to the essentially experimental descriptive term "anaphylaxis". Today it was used in the general sense to include all conditions in which immunological sensitization reactions were the basis of the observable reactions. In that third phase, therefore, another branch of science had been developed, termed "allergy". Once again, in the space of a few years, certainly no more than 10 from the formulation of anaphylaxis by Richet in 1902, almost, if not all, the basic concepts in that new science had been discovered. With regard to asthma, there now existed an explainable ætiology in terms of an immuno-

logical mechanism, precise methods of skin testing for determining specific causal allergens could be applied and, as a consequence, methods of desensitization could be formulated. Those facts constituted the major fundamental advance made in the asthma syndrome at any time. Their value today, after half a century, was still basically unchallengeable, in spite of several other primary ætiological causes put forward (especially the psychogenic). Experimentally in animals, and clinically in many allergen-sensitive asthmatics, one could induce an attack by over-dosage with the specific allergen almost at will; that could not be done consistently, if at all, by other means.

Dr. Prentice said, in conclusion, that one point which was often raised, and rightly so, in reference to the treatment of asthma, was the value of skin tests and desensitization procedures. Anomalous findings did occur, as two examples would show. (i) In a minor proportion of patients, in whom one would expect from the clinical data to obtain positive reactions on full skin testing, the results were completely negative; in such patients skin sensitization was absent, although undoubtedly shock tissue sensitivity was present and reactions occurred with the offending allergen, so that desensitization could not be attempted. (ii) In another larger group, skin reactions were positive, and often markedly so, yet desensitization did not produce significant improvement. In that group other aggravating factors had become predominant, particularly respiratory tract infection and psychogenic causes, and the basic treatment had to be directed towards them. Those types unresponsive to immunological treatment, and others, did occur, and were known and accepted by allergists. They did not alter the significance of the sensitization or allergic ætiology as the important basis for the causation of symptoms in the majority of asthmatics. There accurate skin test procedures were required. One fact should be emphasized, because its misinterpretation was the greatest reason for scepticism concerning the value of tests and desensitization treatment—namely, that the interpretation of reactions in the light of the clinical history and examination must be accurate always. When that was done, then the following desensitization procedures produced the greatest statistical and clinically significant improvement of any type of treatment.

DR. IVAN MAXWELL stressed the importance of avoidance of allergens, especially house dust, and said that it was ideal for asthmatics sensitive to house dust to sleep out on a veranda. In the injection treatment of asthma over-dosage was common, and that led to confusion regarding the benefits of desensitization. He thought that the moderate use of adrenaline as a spray was a valuable method of treatment of asthma. He questioned the importance of milk as an allergen.

DR. GERALD DOYLE said that in milk allergy there was species sensitivity to albumin, and those affected by cow's milk could often tolerate goat's milk. Those sensitive to casein were non-species-sensitive and would not tolerate any form of milk.

DR. S. WIENER said he thought that the tone of smooth muscle in the bronchial tree was very important in asthma.

DR. S. BRAND said he considered the use of adrenaline spray was deleterious, and also spoke of the use of aminophyllin.

DR. M. MARTIN referred to the administration of adrenaline, emphasizing the point that if repeated doses were necessary, they should be given at different sites.

## Out of the Past.

*In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.*

### THE OVERCROWDING OF THE PROFESSION IN AUSTRALIA.[1]

[From the *Australasian Medical Gazette*, June, 1890.]

We again feel it our duty to warn practitioners in older countries not to think that Australia is still the Eldorado for medical men it once was. The number of medical men in the Australasian colonies is now very great, and as a consequence professional competition is perhaps even more severe than in Europe and the United States. As a proof of this we may say that there were recently 78 applications by properly qualified men for the appointment of resident medical officer to the private hospital of a single mining company, the successful candidate being a practitioner already locally resident.

[1] From the original in the Mitchell Library, Sydney.

## Correspondence.

### LOURDES CENTENARY.

SIR: In THE MEDICAL JOURNAL OF AUSTRALIA dated March 8, 1958, there appeared a letter by L. D. Renouf under the above-named heading.

I trust the writer will pardon me for following up his letter with some details added in the cause of general knowledge.

The mention of "Lourdes" seems automatically to bring to the mind the word "miracle". There is an exact precise procedure for the examination of claims of miraculous cures, and there have been many recent publications on this matter. These include one by Dr. F. B. McCann, who, during a visit to Lourdes a few years ago, was made a member of the Medical Association at Lourdes.

The quoted figure of 1200 inexplicable cures accepted by the Medical Bureau dealing with these cases is correct as far as that information goes, but the investigations do not end at this stage. Twelve months later a further investigation is made by the Medical Bureau.

If the case is still inexplicable on either natural or scientific grounds, it is referred to an international medical commission; one in 1955 was composed of 26 doctors, of whom 10 were professors of medicine. Doctors of any faith may and do become members of the various boards of investigation.

If the case passes this international board it is referred to a canonical commission for a final declaration.

The working of this commission is along the lines that the cure cannot be explained by natural causes and declares it a miraculous cure. Such declaration has no binding effect on any of the doctors who composed the various boards of investigation.

The present position is that by 1958, the year of the centenary celebrations, 50 cases have been finally accepted.

Yours, etc.,

J. M. FLATTERY.

18 Malvern Avenue,
Croydon,
New South Wales.

March 27, 1958.

### EPISIOTOMY.

SIR: One doubts whether the argument for and against episiotomy will ever be resolved, and hopes indeed that it will not. Few will deny that episiotomy has its place, but argument is stimulating. I find that ten years in general practice have produced a conservative attitude, and a growing respect for Nature's provision. Others with greater experience are doubtless more inclined still to this attitude. The capacity of the perineum to dilate is undoubtedly increased by the accoucheur continuing to imitate Nature. That is to say, even after induction of anæsthesia, the head is made to advance and retire in a "tidal" manner until delivered. Dr. Hodgkinson has referred to this (M. J. AUSTRALIA, March 15), and it can, of course, be achieved when desired without resort to the obstetric forceps. Sometimes a perineal tear results, but what of that? It produces a symmetrical wound, whereas episiotomy does not. Careful repair of all layers with fine (repeat fine) catgut, including if need be the *sphincter ani*, produces a result as good as that of any episiotomy. Haphazard insertion of "through and throughs" has no place in a mid-line tear. One treats it with the same care as that given to a posterior colpoperineorrhaphy. One notes also how much happier mothers are if skin edges can be approximated by well-placed interrupted subcuticular catgut sutures, and skin sutures omitted altogether. They are spared the discomfort of sitting on "bits of wire", and the ordeal of having them dug out of

their grooves as they are removed. The objection that the buried catgut becomes infected is, in my experience, academic. As to the end result, nothing has yet been said of the levator muscles. Surely active contraction of these should be instituted as a post-natal exercise for every patient.

Yours, etc.,

P. W. GILL.

Dangar Road,
Singleton,
New South Wales.
March 27, 1958.

## NEPHRITIS IN QUEENSLAND.

SIR: I was most interested in the article by Dr. D. A. Henderson on the ætiology of chronic nephritis in Queensland. Coming from Victoria in 1919 to the Hospital for Sick Children as senior resident medical officer, I was impressed immediately by the number of children suffering from lead poisoning and nephritis. I had the privilege of working under Dr. Jeffris Turner and Dr. Lockhart Gibson. Dr. Turner had devoted much of his life to investigating the causes of these diseases amongst children. His approach to the problem was that of keen observation, sterling common sense and enthusiasm. Toddlers and very young children seemed to be those most frequently affected, and most of them were finger-suckers or nail-biters. I well remember having to note down the affected fingers and nails of these children. Dr. Turner noticed that most Queensland houses were surrounded with verandas, where children spent most of their time, and learnt to walk by grasping the rails. He then found that the white paint crumbled in the hot sun and the children received frequent doses of lead. Practically all the rails were painted with a white lead paint. He and Dr. Gibson initiated the campaign to forbid the use of lead in any paint within the reach of children. Dr. Turner was supported by other pædiatricians, but it was thirty years before the legislation was passed. In 1919 the grand old man, "Daddy Turner", as he was affectionately called, feared that the battle was lost, so there was great rejoicing when the law was finally passed a few years later. Queensland owes much to these men who fought business interests and public apathy and eventually prevailed.

Yours, etc.,

E. KENT-HUGHES.

137 Faulkner Street,
Armidale,
New South Wales.
March 31, 1958.

# Post-Graduate Work.

## THE MELBOURNE MEDICAL POST-GRADUATE COMMITTEE.

### PROGRAMME FOR MAY, 1958.

### Refresher Course in General Medicine and Surgery.

A REFRESHER COURSE for general practitioners, drawn up by the Committee in consultation with the Victoria Faculty of the College of General Practitioners, will be held in Melbourne from April 28 to May 3, 1958.

Monday, April 28, at St. Vincent's Hospital, Victoria Parade, Fitzroy: 9.30 a.m., "The Use of Diuretics", Dr. Maurice Clarke; 11 a.m., "Psychosomatic Medicine in General Practice", Dr. H. J. B. Stephens and Dr. Luke Murphy; 2 p.m., ward round conducted by Dr. T. A. F. Heale; 4 p.m., "Management of Diabetes in General Practice", Dr. W. Hamilton Smith.

Tuesday, April 29, at St. Vincent's Hospital: 9.30 a.m., "The Place of Tranquillizers in Therapy", Dr. James F. Hughes; 11 a.m., "The Use of Deep X-Ray Therapy", Dr. J. P. Madigan; 2 p.m., ward round conducted by Professor John Hayden; 4 p.m., quiz session, Professor John Hayden.

Wednesday, April 30 (morning), at the Infectious Diseases Hospital, Fairfield: Clinical demonstration by the hospital staff.

Wednesday, April 30 (afternoon), at the Royal Children's Hospital, Pelham Street, Carlton: 2 p.m., "The Use of Antibiotics in Common Infections in Children", Dr. Stanley Williams; 3 p.m., "Surgical Emergencies in the Newborn", Mr. N. A. A. Myers; 4 p.m., quiz session (panel, Dr. Mostyn Powell and Mr. Peter G. Jones).

Thursday, May 1, at the Alfred Hospital, Commercial Road, Prahran: 9.30 a.m., "Rectal Bleeding", Mr. James Guest; 11 a.m., "Backache", Mr. C. McNeur; 2 p.m., ward rounds conducted by Mr. H. A. Phillips and Mr. G. L. Grove; 4 p.m., "Urological Problems", Mr. Kennedy Burnside.

Friday, May 2, at the Alfred Hospital: 9.30 a.m., "Head Injuries", Mr. K. C. Bradley; 11 a.m., "Hernia", Mr. Ian McVey; 11.50 a.m., "Varicose Veins", Mr. Kendall Francis; 2 p.m., quiz session (chairman, Mr. James Guest; panel, Professor M. Ewing, Messrs. C. A. M. Renou, G. L. Grove, N. T. Hamilton and R. S. Lawson); 3.45 p.m., "Hand Injuries and Infections", Mr. John Snell.

Saturday, May 3, at the Eye and Ear Hospital, Victoria Parade, East Melbourne: 9.30 a.m., "Demonstrations of E.N.T. Cases of Interest to General Practitioners", conducted simultaneously by Messrs. C. N. Cantor, W. Williams, D. F. O'Brien, R. F. Stevens and C. B. Napier; 9.30 a.m., "Bucco-Pharyngeal Cancer", Mr. E. E. Dunlop; 9.30 a.m., "Demonstration of Cases of Squint", Dr. F. G. Fenton; 9.30 a.m., "Eye Cases of Interest to General Practitioners", Dr. E. D. O'Brien; 9.30 a.m., "Medical Cases Exhibiting Optic Atrophy", Dr. John Billings; 9.30 a.m., "Allergy in Relation to Eye, Ear, Nose and Throat Cases", Dr. Sol Brand; 11.15 a.m., "Colour Transparencies of Ocular Disease", Dr. Kelvin Lidgett; quiz session.

Enrolments on the Committee's forms should be sent to the office of the Melbourne Medical Post-Graduate Committee at 394 Albert Street, East Melbourne, by April 14. The fee for the course, from Monday to Friday inclusive, is £9 9s. The clinical meeting at the Eye and Ear Hospital is without fee and open to all members of the medical profession.

### Lectures in the Scientific Basis of Medicine.

As previously announced, a series of lecture discussions in cardio-pulmonary physiology will commence in May, and will be conducted at 8 p.m. in the Main Lecture Theatre, Royal Melbourne Hospital. All members of the medical profession are invited without fee. Topics to be discussed in May are: Friday, May 2, "Vascular Responsiveness in Hypertension", Dr. A. Doyle; Friday, May 23, "Œdema and the Problem of Aldosterone Production", Dr. D. A. Denton.

### Course in Forensic Medicine.

Commencing on May 19, Dr. Keith Bowden, on behalf of the Post-Graduate Committee, will conduct a course designed in particular for country doctors, with emphasis on the performance of autopsies of interest to the coroner. Practical work will be performed under supervision. This course will be held from 9.30 a.m. each morning for two weeks at the Coroner's Department, Flinders Street Extension. There will be no fee. Enrolments should be sent to the Post-Graduate Committee.

### Courses for Higher Qualifications.

*Course in Medicine.*—A course in medicine suitable for candidates for M.R.A.C.P. and M.D. II will commence at Prince Henry's Hospital on May 26. Details of this course are published in another column.

*Course in Radiodiagnosis.*—A course in radiodiagnosis will commence in May, provided sufficient enrolments are received by May 2. Those interested should contact the Committee immediately.

Courses in anatomy, physiology, pathology, microbiology and physics, which commenced earlier, will continue.

In June a course in oto-rhino-laryngology and special pathology, suitable for D.L.O. candidates, will commence, and on June 30 a course in pathology, suitable for primary F.R.A.C.S. candidates.

*Course in Psychiatry.*—A course in psychiatry, suitable for D.P.M. candidates or interested medical graduates, will be conducted by the Australasian Association of Psychiatrists (Victorian State Branch) on Thursday evenings at 8.15 p.m. at the Royal Melbourne Hospital, commencing June 12. The fee will be £10 10s.

### Country Courses.

*Bendigo.*—Friday, May 2, at Lister House, 37 Rowan Street, at 8 p.m.: "Diagnosis and Management of Abdominal Pain", Dr. R. Andrew. Local secretary, Dr. A. J. Walters, 514 High Street, Golden Square, Bendigo.

*Ballarat.*—Thursday, May 22, at Craig's Hotel, at 8 p.m.: "Surgery of Hand Reconstruction", Mr. B. K. Rank. Local secretary, Dr. N. Pescott, 626 Sturt Street, Ballarat.

*Mortlake.*—Saturday, May 31: 3.45 p.m., "Anæmia in Pregnancy", Dr. J. H. Bolton; 5.15 p.m., "Diagnosis and Treatment of Retention of Urine", Mr. A. B. Alder. Local secretary, Dr. R. R. Sobey, 6 Spence Street, Warrnambool.

Fees for the above courses are at the rate of 15s. per lecture, but those who have paid an annual subscription to the Committee are invited to attend without further charge.

### Flinders Naval Depot.

On Wednesday, May 14, at 2.30 p.m., Dr. Ian McKay will talk on "Problems Associated with Chronic, Active and Recurrent Hepatitis". This lecture will be given by arrangement with the Royal Australian Navy.

### Overseas Lecturers.

Professor J. H. Gaddum, Professor of Pharmacology, University of Edinburgh, author of the well-known textbook, will visit Melbourne from May 17 to 24. The Post-Graduate Committee hope to arrange for a lecture at the B.M.A. Hall on Thursday, May 22, at 8.15 p.m., and will announce details as soon as possible.

Professor M. L. Rosenheim, Sims Commonwealth Travelling Professor, will deliver a lecture open to the medical profession at 8.15 p.m. on Thursday, May 15, at the B.M.A. Hall on "Chronic Pyelonephritis". All members of the profession are invited.

### Information.

The address of the Melbourne Medical Post-Graduate Committee is 394 Albert Street, East Melbourne. Telephone: FB 2547.

## PRINCE HENRY'S HOSPITAL, MELBOURNE.

### Post-Graduate Course in Medicine, 1958.

THE honorary medical staff of Prince Henry's Hospital, Melbourne, will conduct a post-graduate course in medicine, suitable for candidates studying for the degrees of M.D. (Melbourne) and M.R.A.C.P. This course will run for eight weeks from May 26 to July 19, 1958. Sessions will be held each day from noon to 1 p.m. and from 2 p.m. to 5.15 p.m. Sessions will also be held from 9.30 a.m. to noon on Saturdays.

During the last four weeks of the course the hospital has invited Dr. M. D. Milne, M.D., M.R.C.P., Physician and Lecturer, London Post-Graduate Medical School, to be present as a visiting lecturer. Dr. Milne is particularly interested in renal diseases, fluid and electrolyte imbalance, aldosteronism and physico-chemical aspects of pharmacology. Dr. Milne will carry out bedside teaching rounds and lecture during the course, visit other hospitals in Melbourne and give lectures to the general medical body. He will also visit medical centres in other States.

Four afternoons a week will be devoted to lectures and case presentations. Members of the class will present to the physician cases examined in the mornings. Discussion of the case will follow. Sometimes this procedure will be varied by the physician in charge by clinico-pathological presentations of cases from his ward or out-patient clinic. Didactic lectures followed by discussion will occupy the latter portion of these afternoons. Wednesday afternoons will be occupied by the presentation of pathological specimens and demonstrations in certain branches of medicine. The morning sessions will be occupied by pathology, ophthalmology, dermatology, electrolyte physiology, allergy, industrial medicine, medical radiology, electrocardiography, etc. Eight seminars on medical subjects have been arranged for Saturday mornings.

Applications for enrolments, together with the fee of £15 15s., should be sent to the Melbourne Medical Post-Graduate Committee, 394 Albert Street, East Melbourne, by May 12, 1958.

# Public Health.

## NATIONAL ASSOCIATION FOR THE PREVENTION OF TUBERCULOSIS IN AUSTRALIA.

THE annual meeting of the National Association for the Prevention of Tuberculosis in Australia was held in Hobart in March. The Council of the Association also met and discussed matters concerning the part the Association takes in tuberculosis prevention and control in this country.

The Council resolved that "N.A.P.T.A. views with alarm what seems to be public, and even professional ignorance of the menace that still exists in regard to tuberculosis, still the most important infectious disease in Australia". It was further resolved: "That every effort be made to ensure that adequate teaching is given in all Australian medical schools, both at undergraduate and graduate levels, in tuberculosis control and prevention." The opinion was expressed that tuberculosis has, to some degree, been divorced from general practice and the main stream of medicine.

The resolutions were the result of the concern expressed by councillors from all States at the growing attitude that the fight against tuberculosis is all but over. While it is true that the death rate continues to fall, it is also true that a considerable number of new cases continue to be found. It was also stressed that just north of Australia there are a number of countries where the death rate from the disease is still extremely high. The over-all picture is that means still exist for the dissemination of tuberculosis in Australia and the possible ultimate creation of strains resistant to current antibiotics.

At the annual meeting it was resolved to retain the name "NAPTA", but to extend the objectives of the Association to include thoracic diseases in general, thus following the example of national voluntary associations in many other parts of the world. Cancer of the lung was mentioned as an example of a lesion particularly calling for attention in this field.

It was reported that NAPTA has been made a member of the Eastern Regional Committee of the International Union against Tuberculosis and that a NAPTA representative is one of the six members of the Union's special subcommittee on rehabilitation.

# Naval, Military and Air Force.

## APPOINTMENTS.

THE following appointments, changes etc. are published in the *Commonwealth of Australia Gazette*, No. 15, of March 20, 1958.

### NAVAL FORCES OF THE COMMONWEALTH.

### Permanent Naval Forces of the Commonwealth (Sea-Going Forces).

*Appointment.* — Surgeon Commander James Edward Davenport is appointed on loan from the Royal Navy, with seniority in rank of 16th April, 1945, dated 1st March, 1958.

### Citizen Naval Forces of the Commonwealth.

*Royal Australian Naval Reserve.*

*Transfers to the Retired List.*—The following are transferred to the Retired List: Surgeon Commander Clifford Kelvin Churches, dated 18th November, 1957; Surgeon Lieutenant-Commander Alan John Gray, dated 26th November, 1957; Surgeon Lieutenant-Commander Graeme Alvin Robson, dated 16th December, 1957.

*Termination of Appointments.*—The appointments of Kenneth Ivor Digwood and Lyn Harley Draper Pearcy as Surgeon Lieutenants are terminated, dated 30th November, 1957.

### AUSTRALIAN MILITARY FORCES.

### Citizen Military Forces.

*Northern Command.*

*Royal Australian Army Medical Corps (Medical).*—2/104175 Captain N. R. Scott-Young is appointed from the Reserve of Officers, 20th November, 1957. 1/39201 Captain R. L.

Thomson relinquishes the provisional rank of Captain, 8th December, 1957, is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Northern Command), and is granted the honorary rank of Captain, 9th December, 1957. The provisional appointment of 1/39192 Captain H. A. Muir is terminated, 19th December, 1957. To be Captain (provisionally), 20th December, 1957: 1/39192 Henry Andrew Muir.

*Eastern Command.*

*Royal Australian Army Medical Corps (Medical).*—2/206960 Major H. O. G. Selle is appointed from the Reserve of Officers, and is appointed to command 1st General Hospital, and to be Lieutenant-Colonel, 1st January, 1958. The provisional rank of F2/1217 Captain D. G. Greening is confirmed. 6/9022 Captain J. Oliver is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Eastern Command), 2nd December, 1957. To be Captain (provisionally), 17th January, 1958: 2/79296 John Churchill Crakanthorp.

*Central Command.*

*Royal Australian Army Medical Corps (Medical).*—4/32074 Captain (provisionally) A. J. Day is seconded whilst undergoing post-graduate studies in the United Kingdom, 1st January, 1958.

### Reserve Citizen Military Forces.

*Royal Australian Army Medical Corps (Medical).*

*Southern Command.*—To be Honorary Lieutenant-Colonel, 22nd January, 1958: Donald James Stevens. To be Honorary Captains: Graham Edward Carroll, 9th November, 1957, and John Anthony Hayman, 6th January, 1958.

The following officers are placed upon the Retired List (Northern Command) with permission to retain their rank and wear the prescribed uniform, 1st March, 1958:

*Northern Command.*—Honorary Captain A. J. Canny is retired, 1st March, 1958.—(Ex. Min. No. 20—Approved 11th March, 1958.)

## The Royal Australasian College of Physicians.

### VICTORIAN STATE COMMITTEE.

The Victorian Fellows and Members of the Royal Australasian College of Physicians will hold a scientific meeting at the Royal Children's Hospital on Saturday, May 3, 1958. The programme will be as follows:

11.30 a.m., "Prevention of Epidemics by Immunization", Dr. E. V. Keogh. 12 noon, "Infectious Mononucleosis: Clinical Aspects, Laboratory Aspects, Epidemiology", Dr. John Forbes, Dr. Allan Ferris, Dr. E. V. Keogh. 1.45 p.m., "Abnormal Sex Differentiation in Children", Dr. Howard Williams. 2.15 p.m., "Some Observations on Virus Infection of the Respiratory Tract in Children", Dr. John Perry. 2.45 p.m., "Indications and Management of Tracheostomy", Dr. A. Venables. 3.45 p.m., "Measles Encephalitis", Dr. H. McLorinan. 4.15 p.m., "Some Observations on Diarrhœa in Infancy", Dr. Max Robinson.

## College of General Practitioners.

### WESTERN AUSTRALIAN FACULTY.

A clinical meeting of the College of General Practitioners, Western Australian Faculty, was held at Bunbury during the week-end November 9 and 10, 1957. The members of the Post-Graduate Committee were gratified by the encouraging response of the general practitioners, and particularly by the interest shown by country members.

On Saturday afternoon Professor N. F. Stanley gave a lecture on "Immunization", which was supported by slides. On Sunday morning Professor E. G. Saint discussed "Recent Advances in Medicine", with special reference to (i) the use

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED MARCH 29, 1958.[1]

| Disease. | New South Wales. | Victoria. | Queensland. | South Australia. | Western Australia. | Tasmania. | Northern Territory. | Australian Capital Territory. | Australia. |
|---|---|---|---|---|---|---|---|---|---|
| Acute Rheumatism | .. | 3(3) | 4 | .. | .. | .. | 1 | .. | 8 |
| Amœbiasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Ancylostomiasis | .. | .. | 6 | .. | .. | .. | 1 | .. | 7 |
| Anthrax | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Bilharziasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Brucellosis | .. | 2(1) | .. | .. | .. | .. | .. | .. | 2 |
| Cholera | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Chorea (St. Vitus) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Dengue | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Diarrhœa (Infantile) | 6(1) | 23(19) | .. | .. | .. | .. | 1 | .. | 30 |
| Diphtheria | .. | .. | .. | .. | 1(1) | .. | .. | .. | 1 |
| Dysentery (Bacillary) | .. | 1(1) | 2(1) | .. | 4(2) | .. | 7 | .. | 14 |
| Encephalitis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Filariasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Homologous Serum Jaundice | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Hydatid | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Infective Hepatitis | 49(27) | 23(10) | 6 | 2(1) | 12(1) | 1 | 2 | .. | 95 |
| Lead Poisoning | .. | .. | 1 | .. | .. | .. | .. | .. | 1 |
| Leprosy | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Leptospirosis | .. | .. | 1 | .. | .. | .. | .. | .. | 1 |
| Malaria | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Meningococcal Infection | 3(3) | .. | 2(1) | .. | .. | .. | .. | .. | 5 |
| Ophthalmia | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Ornithosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Paratyphoid | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Plague | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Poliomyelitis | 1 | .. | .. | .. | .. | .. | .. | .. | 1 |
| Puerperal Fever | .. | .. | 1 | .. | .. | .. | .. | .. | 1 |
| Rubella | .. | 29(15) | .. | 2 | 9(6) | .. | .. | .. | 40 |
| Salmonella Infection | .. | .. | .. | 3(3) | 2(2) | .. | .. | .. | 5 |
| Scarlet Fever | 20(9) | 14(9) | 2 | 1(1) | 4(3) | .. | .. | .. | 41 |
| Smallpox | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Tetanus | .. | 1(1) | .. | .. | 1(1) | .. | .. | .. | 2 |
| Trachoma | .. | .. | .. | .. | 59(1) | .. | 1 | .. | 60 |
| Trichinosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Tuberculosis | 9(5) | 22(17) | 10(8) | 4(4) | 9(8) | 4(1) | .. | 1 | 59 |
| Typhoid Fever | .. | 1 | .. | .. | 1(1) | .. | .. | .. | 2 |
| Typhus (Flea-, Mite- and Tick-borne) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Typhus (Louse-borne) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Yellow Fever | .. | .. | .. | .. | .. | .. | .. | .. | .. |

Figures in parentheses are those for the metropolitan area.

of "Ansolysen" in the treatment of hypertension, (ii) nephritis, its classification and treatment, and (iii) cirrhosis of the liver. Dr. D. J. R. Snow then read a paper on "Disease Patterns in Families", in which he deplored the fact that general practitioners in Australia did not record familial disease patterns as frequently as they should.

## The College of Radiologists of Australasia.

### EXAMINATION RESULTS.

The following candidates were successful in the March, 1958, examinations of the College of Radiologists of Australasia, Part I, for membership of the College:

Radiodiagnosis: Dr. D. R. Gibson (New Zealand), Dr. R. M. Chrisp (New Zealand), Dr. J. A. Lyall (New South Wales), Dr. W. R. Vautin (New South Wales).

Radiotherapy: Dr. B. W. McEwen (New South Wales), Dr. Thelma Johnson (Tasmania), Dr. R. G. Bourne (Queensland).

## Australian Medical Board Proceedings.

### TASMANIA.

The following have been registered, pursuant to the provisions of the *Medical Act*, 1955, of Tasmania, as duly qualified medical practitioners: Elliott, Margaret Helen, M.B., B.Ch., 1922 (Queen's Univ., Belfast); Chapman, Robert James, M.B., B.S., 1957 (Univ. Sydney); Davies, Anne Louise, M.B., B.S., 1957 (Univ. Sydney); Kidd, James Douglas, M.B., B.S., 1957 (Univ. Sydney); Mitchell, Trevor Ashton, M.B., B.S., 1957 (Univ. Sydney); Roebuck, David John, M.B., B.S., 1955 (Univ. Sydney); Gurr, Frederick William, M.B., B.S., 1956 (Univ. Melbourne); Sachdev, Avtar Singh, M.B., B.S., 1956 (Univ. Sydney); Rodan, Brian Alexander, M.B., B.S., 1955 (Univ. Melbourne).

The following have been provisionally registered, pursuant to the provisions of Section 14A of the *Medical Act*, 1955, of Tasmania, as duly qualified medical practitioners: Begent, Judith Mary, M.B., B.S., 1957 (Univ. Melbourne); Capp, Graham Hadley, M.B., B.S., 1957 (Univ. Melbourne); Childs, Clive Inskip Varney, M.B., B.S., 1957 (Univ. Melbourne); Duras, Eva Marianna, M.B., B.S., 1957 (Univ. Melbourne); Kloss, Michael, M.B., B.S., 1957 (Univ. Melbourne); Rayner, George Halyer, M.B., B.S., 1957 (Univ. Melbourne); Lucas, Lorna Mary, M.B., B.S., 1957 (Univ. Sydney); Tresize, Geoffrey Frank, M.B., B.S., 1957 (Univ. Melbourne); Kidson, Malcolm Anderson, M.B., B.S., 1957 (Univ. Melbourne); Killmier, Roger W., M.B., B.S., 1957 (Univ. Melbourne); Smith, Philip Brian, M.B., B.S., 1957 (Univ. Melbourne); Yuen, Wai Mun, M.B., B.S., 1957 (Univ. Adelaide).

## Medical Appointments.

Professor W. V. Macfarlane has been appointed a member of the Council of the Queensland Institute of Medical Research.

## Nominations and Elections.

The undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

White, Francis David, M.B., B.S., 1952 (Univ. Sydney), 110 Myall Street, Oatley, New South Wales.

Dichne, David, M.D., 1927 (Univ. Leipzig) (registered in accordance with the provisions of Section 17 (2A) of the *Medical Practitioners Act*, 1938-1957), Broughton Hall Psychiatric Clinic, Wharf Road, Leichhardt, New South Wales.

Whelan, James Joseph, M.B., B.S., 1955 (Univ. Sydney), 71 St. John's Avenue, Wollongong, New South Wales.

## Deaths.

The following deaths have been announced:

Spencer.—John Clark Spencer, on March 29, 1958, at East Malvern, Victoria.

Furber.—Thomas Maynard Furber, on April 2, 1958, at Sydney.

Struan-Marshall.—John Laurance Struan-Marshall, on April 6, 1958, at Springwood, New South Wales.

## Diary for the Month.

April 22.—New South Wales Branch, B.M.A.: Hospitals Committee.
April 23.—Victorian Branch, B.M.A.: Council Meeting.
April 24.—New South Wales Branch, B.M.A.: Branch Meeting.
April 24.—South Australian Branch, B.M.A.: Listerian Oration.
April 24.—Queensland Branch, B.M.A.: Council Meeting.

## Medical Appointments: Important Notice.

Medical practitioners are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

*New South Wales Branch* (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales. Anti-Tuberculosis Association of New South Wales.

*South Australian Branch* (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

## Editorial Notices.

All articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

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